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PERSISTENT MEMORY DEFECT FOLLOWING ENCEPHALITIS[1]

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THIS paper will describe 4 cases in which, following what appeared to be an encephalitis of non-specified ætiology, the patient recovered, but with a permanent defect of intellectual function comprising a severe impairment of recent memory with a long period of amnesia, including not only the illness and subsequent events but several years before the illness. The defect of recent memory was in all cases out of proportion to impairment of other intellectual functions, which indeed in the patients least severely affected were little if at all interfered with. Immediate retention of test material was unaffected, and skills and knowledge acquired before the illness were well preserved. The clinical picture, therefore, was of a very unusual kind, the patient being able to make a relatively good score on the usual batteries of intelligence tests but failing, as a rule completely, on those items that are designed to assess recent memory. The bizarre character of the syndrome had in some instances given rise to the diagnosis of hysteria.

Case I

Summary.—A man aged 30 at the end of March 1947, had an acute febrile illness with a convulsive seizure. A week later he was afebrile, but confused, with a lymphocytic pleocytosis in the cerebrospinal fluid. There were no signs of meningitis or of a focal cerebral lesion. He was left with a retrograde amnesia of two years, and a severe defect of recent memory, and some disorientation in time and space, but retained skills and knowledge acquired before the illness. In the course of the next nine years there was slight improvement. The retrograde amnesia persisted. The defect of recent memory remained disabling.

P. E. aged 30, was first seen by one of us (C. P. S.) on January 28, 1948.

When asked what he was complaining of he said, "There's nothing wrong with me physically but mentally things as they happen don't seem to impress themselves on my mind. For example, I couldn't tell you whether I cleaned my teeth or not

[1]Part of the material in this paper was presented in the Hughlings Jackson Memorial Lecture of the Montreal Neurological Institute, delivered by Sir Charles Symonds on May 11, 1960.

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this morning. I can't clearly remember coming to London today, although I know I did, but I couldn't tell you whether I came by train or car."

There was no family history of nervous or mental illness.

The past history as related by himself was uneventful except that as a child he was shy and nervous and unhappy at his preparatory school, where he was bullied. At his public school he was backward at his work but interested in artistic pursuits and music. He was above average at games. After leaving school he was put to work in a bank but disliked it and joined the Merchant Navy, being a volunteer in the Royal Naval Reserve at the same time. He was called up at the outbreak of war and posted to India, where he served continually at sea and on shore, attaining the rank of Lieutenant-Commander. Early in 1945 he contracted malaria, after which he suffered from headaches and was sent to Kashmir on sick leave. Following this he returned to his ship. He has no consecutive memory of events after this time.

The history obtained from a relative was that since boyhood he had always been excitable, nervous and inclined to exaggerate, and that before the present illness he was unreliable in his statements.

After his return home at the end of the war he went into partnership with a friend in an export business and was taken ill while in Brussels.

Present illness.—He was admitted to St. Mary's Hospital on April 5, 1947, under the care of Dr. Denis Brinton, who has kindly given us access to the hospital notes. The history was that fourteen days previously he had been taken ill in Brussels with a sore throat and fever. On the fourth day of his illness he complained of headache and then had a convulsive seizure. He was said at that time to have had no abnormal physical signs, and the fluid obtained by lumbar puncture was reported to have been normal. On admission to St. Mary's he was afebrile and fully conscious, but unable to give any account of himself, his whereabouts or past history. No abnormal physical signs were observed. He was discharged on June 27, 1947, at which time there was reported to have been improvement in that his memory of past events was quite clear. The cerebrospinal fluid findings were as follows.

Date	*Cells per c.mm.*	*Protein mg. per cent*
April 6	300 lymphocytes	120
April 14	70 lymphocytes	120
April 23	150 lymphocytes	—
May 9	60 lymphocytes	—
May 27	4 lymphocytes	80

The Wassermann reaction was negative in the specimen taken on April 6. A blood count on April 6 showed 100 Hb. per cent; R.B.C. 5,100,000 c.mm.; W.B.C. 8,800 c.mm.; Neutrophils 62 per cent; lymphocytes 32 per cent; mononuclears 6 per cent.

The examination on January 28, 1948, revealed no physical signs of any organic disease either in the nervous system or elsewhere. There was no dysphasia or dyspraxia. His manner was polite and his behaviour normal. There was no affective disorder. He was no more than naturally anxious about his defect of memory and consequent inability to lead a normal existence. He stated that his memory for past events was unimpaired up to some time in 1945 and gave a consecutive account of his life history (later confirmed by relatives), including the events of the war, ending with the memory of the last ship he had served in. He had no recollection of his illness in 1947, nor could he say when it had occurred or give any consecutive account of what he had been doing since that time. He consistently retained 6 digits, but on being tried with 7 twice failed by transposing the order. In the serial 7 subtraction test he was slow (90 secs.) with two errors. In the Name, Address and Flower test

at the end of five minutes he repeated the name correctly, could not remember any item of the address, and when asked whether there was any third thing he had been asked to remember, denied it.

He was admitted to The National Hospital, Queen Square, on June 7, 1948, where the absence of abnormal physical signs was confirmed. An EEG showed no abnormality. The examination of the blood was normal and the Wassermann test negative. The cerebrospinal fluid was under a pressure of 130 mm. and was clear and colourless with 1 lymphocyte per c.mm., 20 mg. of protein per cent, negative Pandy and Nonne-Apelt tests, no change in the colloidal curve (Lange) and a negative Wassermann reaction. Radiograms showed no abnormality in the skull nor any calcified cysts in the muscles. His general behaviour in the ward was normal during his month's stay. He was pleasant and sociable, alert and anxious to co-operate. There was no evidence of mood disorder or special preoccupations other than a natural concern with his disability. He was inclined, however, to be somewhat childish in his manner and to make fatuous jokes, suggesting a very mild organic personality change.

Psychological examination confirmed that he was able to recall in adequate detail his early days and his adult life up to a time about two years before his illness. From this time onward his memories were vague, uncertain and disconnected. He remembered, for example, addressing some soldiers before returning home in the "Georgic" after the Japanese surrender, but had no recollection of the journey home except arriving at Edinburgh, and subsequently when he arrived at his own village, a notice saying "Welcome Home from Burma" put up by some local children. Thereafter he recollected having combined with a friend to set up business in an Export Agency. These memories, however, were isolated fragments, the loss of memory for this period of his life being almost complete.

Formal tests gave the following results. In the serial 7 test he was correct in the first 6 responses and then changed to subtracting 5 to the end of the series. He retained 8 digits forward and 4 backwards. Mental calculations were done quickly and correctly. His interpretation of similarities was without error. In tests of general knowledge he named the Prime Minister and his two predecessors correctly, gave the capitals of Spain, Germany and Italy correctly, but was at a loss for that of Portugal. He could name only one Welsh county, and one bridge across the Thames but was able to give the names of three composers and three authors.

At the next examination three days after his admission when asked how long he had been in hospital he said he had no idea. He was uncertain of the month, date and year, but accepted 1948 when it was suggested. He was asked to remember the following, which he repeated aloud (1) Pencil, (2) Blue, (3) 12 Piccadilly. After five minutes he could recall only that there had been three things to remember. The Babcock sentence he failed to repeat correctly after 10 attempts. He always made a complete and sensible sentence, showing that he had understood the gist of it.

In drawing maps and plans of houses and streets his performance was extremely poor in comparison with his educational level. When asked next day if he recognized his map of Africa he said, yes he thought he did and that it was his own drawing, but quite honestly he wasn't sure if he had drawn it a few days ago or last year. He made an adequate drawing of a bicycle.

He was examined on June 17, 1948, by Professor O. L. Zangwill, who reported "On various memory tests this patient reacted in a manner quite typical of a case with a severe organic amnesic syndrome. The main features are (1) grossly impaired retention in all fields; (2) defective recognition with a tendency to paramnesic reduplication; (3) gross errors in recall and learning tests; (4) defects in time relations of recent events; (5) a tendency to stereotyped phrases and evasive rationali-

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zation. The picture suggests a circumscribed amnesic syndrome without confusion or significant intellectual loss."

Professor Zangwill noted that the contrast between his adequate perception and poor retention was well shown when he was asked to describe and interpret a picture and subsequently tested for recall or recognition. For example, when shown the "Telegraph Boy" picture in the Stanford-Binet Intelligence Scale he gave a first class interpretation, but when shown the same picture two minutes later rejected it as unfamiliar on the ground that the vehicle in the "original" picture was a lorry and not a motor car (paramnesic distortion).

A psychometric examination was subsequently carried out by Dr. M. W. Ferguson, who found that the patient had an I.Q. of 113 on the Wechsler-Bellevue Test.

He was seen by Dr. Eliot Slater, who considered that he was suffering from an organic defect but that his past history, particularly the account given by his sister, suggested that he had a hysterical personality. In view of this he questioned whether the circumscribed amnesia of two years before his illness might be a hysterical superstructure and advised that this should be investigated with the aid of sedation and suggestion. Under Dr. Slater's direction this possibility was investigated during an interview conducted under intravenous sedation. There was no improvement of the retrograde amnesia and under the amytal his memory difficulties increased in a way that suggested an organic basis; for example, perseveration became much more marked.

He was again seen (C. P. S.) on February 9, 1949. In the interval he had been living at home with his mother and sister. He was reported to make himself useful in the house and was capable of shopping errands and taking children to school. He had also resumed playing the piano. On examination there was no important change in his condition. His complaint was "Things that are going on don't impress themselves on me. It's the immediate things that go." Asked if he remembered me he replied "In all honesty not your face, but I do recognize your voice and manner." Asked if he read the papers, he said that he did and gave a moderately well-informed, though superficial, account of current world affairs. Questioned about his retrograde amnesia, he said he now knew a good deal about what he did during that period because he had been told it so often, but he did not remember it "as a fact." He spontaneously expressed his wish to take up teaching children as soon as he was fit, but said that at present his inability to remember would prevent this. He went on to say that his memory defect also caused him much embarrassment socially. If, for example, he was asked at lunch what he had been doing that morning and visitors were present, it was simpler to make up a story than to say he did not know. He retained 8 digits, and in subtracting serial sevens from 100 completed the series with one error in 40 seconds. Given a name, address and flower to remember, without repeating them aloud, he could recall no item after five minutes, saying "I remember you did ask me to remember three things and repeating them in my head, but I have concentrated so hard since on the other tests that I've forgotten them."

He was again seen (C.P.S.) on February 4, 1956, nearly nine years after the onset of his illness. He was reported by his doctor to have improved up to the stage of accepting an unpaid job teaching geography and supervising games in a local preparatory school. He stated that he was also giving a few lessons at his home to backward children and teaching the piano, and spoke in a rather boastful way about his success with children with whom others had failed.

Questioned about his period of amnesia, he said there was a complete blank from the end of the war until the end of 1949 or the beginning of 1950. When asked whether he remembered being in the National Hospital (this having been in 1948) he

replied "Yes, but that was quite recently, wasn't it? Yes, I think I do. Was there a room leading into the ward that was a sitting-room?" When told there was, he said "Thank you, well I do remember." Further asked what he now remembered of the post-war period he said "I remember what people have told me about it since, but I don't think I remember it as an event at the time." He gave a consecutive account of the main events in his life during the past year slowly and with hesitation. Concerning the events of the past twenty-four hours he was again hesitant but gave a circumstantial account of his activities.

In the Name, Address and Flower test administered as on the last occasion, he reproduced the name correctly, but made no attempt at the other items. He completed the serial sevens from 100 test in 30 seconds with one error. He retained 8 digits. On this occasion he was able to remember coming up by train to Waterloo and thence by tube to Regent's Park. His sketch plan of his home compared favourably with that done in hospital eight years previously, but his map of Piccadilly Circus was worse.

Case II

Summary.—A man aged 38 in June 1955 had an acute febrile illness with several convulsive seizures, followed by confusion. Cerebrospinal fluid examinations showed a lymphocytic pleocytosis with raised protein, which slowly returned to normal. He was left with a retrograde amnesia, which was patchy for twenty years and dense for eleven years, with a severe defect of recent memory. He was disorientated in time but retained skills and knowledge acquired before his illness. In the ensuing two years he improved, but the retrograde amnesia was unaltered, and the defect of recent memory remained disabling.

Mr. J. D. aged 38 was admitted to the National Hospital, Queen Square, under Dr. E. A. Carmichael on September 2, 1955. He was unable to give any account of himself, and his wife stated that he had been confused for three months. There was no family history of nervous or mental disorder, other than that his paternal grandfather was an epileptic. At the age of 16 he had rheumatic fever, but there was no past history of other significant illness, although he had been liable to occasional severe headaches. He was a farmer by occupation, and a hard worker. There were three healthy children of the marriage.

Present illness.—The history of this was obtained from his wife and the records of the hospital to which he was originally admitted. On June 13, 1955, he complained of malaise and anorexia, and four days later had a severe headache. On the morning of June 19, while at work, he had a brief generalized epileptic seizure. This was followed by five similar attacks during the day. He was delirious during the following night and remained confused for the next twenty-four hours. He was then found to have a temperature of 103° F. and admitted to hospital on June 20. He was there found to be confused, with no abnormal physical signs. His subsequent progress and the results of laboratory investigations are summarized as follows:

Hæmoglobin estimation and white cell count were normal. Agglutination tests for typhoid and paratyphoid were negative, as was blood culture. The serum electrolytes were normal. A lumbar puncture revealed a normal cerebrospinal fluid except for a slightly raised protein (*see* Table I, 1).

In spite of treatment with penicillin and terramycin, his temperature remained elevated at 103° F., but there was improvement concomitant with a course of streptomycin.

A second lumbar puncture performed ten days after the first showed a marked increase in cell and protein content but thereafter these constituents fell to normal (*see* Table I, 2–7). An EEG showed a gross generalized abnormality. Ventriculography showed only slight dilatation of the right lateral ventricle.

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TABLE I.—TABLE OF C.S.F. FINDINGS—CASE II

	Date	*Pressure mm.* H20	*Cells per c.mm.*	*Protein* mg.%	*Pandy*
1	21.6.55	170	5	70	negative
2	1.7.55	135	107	120	positive
3	4.7.55	(ventricular)	104	100	positive
4	11.7.55	160	45	70	positive
5	16.7.55	210	30	80	positive
6	22.7.55	220	7	60	positive
7	6.8.55	210	7	140	positive
8	8.9.55	(A.E.G.)	0	80	(paretic Lange)
9	30.8.57	215	1	75	positive (No change in Lange)

When admitted to the National Hospital the patient was disorientated and showed a severe memory defect for recent events. There were no abnormal physical signs. Investigations, including hæmoglobin, white cell count, and sedimentation rate, were normal. The cerebrospinal fluid (Table I, 8) contained 80 mg.% protein, and the Lange was paretic. The EEG showed generalized slow activity but without focal features. An air encephalogram was normal. He was seen on several occasions by the psychologist (Mrs. E. Warrington), who on October 13, 1955, found that he was confused and disorientated for time and place. He had practically no memory of his life before the time of his illness, and although he remembered he had a wife and children, he could not recall any past events clearly. His immediate memory was less than half a minute. The vocabulary test was above mean, so that he was considered to be at least of average intelligence. He was able to perform tests which required no memory, viz. Block Design, but was unable to score more than half marks on the simplest visual design of the Wechsler Memory Scale and with the more complex ones he had completely forgotten them by the time he came to draw.

On November 19, 1955, he could give an account of events up to about the beginning of the war (1939). When asked his age, he thought it to be in the early twenties (the age he was in 1939). He now knew he was in a London hospital, but his orientation for time had not improved. His score on Block Designs was again average, though a few minutes later he denied having done any. He was able to recall very simple visual designs immediately after having seen them, but had probably forgotten having seen any design at all two minutes later. He was able to work out his age, given the year, and was able to learn a simple sentence in two trials. It was concluded that although he had severe amnesia his powers of reasoning, verbal, visuo-spatial, and abstract, were almost completely intact.

On December 16, 1955, he was unco-operative during psychological testing, becoming querulous and aggressive at almost every question. He still had amnesia up to 1939 and thought he was 25 years of age. For day-to-day events his retention continued to break down after about 30 seconds.

On October 21 he wrote a requested letter to the house physician as follows: "It seems to me that my memory is very distant and practically not recent. I hope that the fact that I am writing a letter means an improvement in my condition. It appears to me that my memory is distant and I do not seem to be able to know anything very recent."

While in hospital he gained insight into his condition, and parallel with this, he at times became aggressive. Serial EEGs showed gradual improvement, so that the record taken on December 16 was virtually normal.

He was admitted for the second time on March 27, 1956. His wife stated that he had improved. He spent most of the day going round the farm and would talk to his men, answering their questions sensibly and agreeably when spoken to. If she went with him to a field, he could tell her exactly what needed doing, but five minutes later had forgotten all about it. He was able to drive a tractor skilfully and find his own way round the farm, but could not remember a conversation for more than a minute or two. He remembered the names of old friends but not those he had met in the last year or two. He had phases in which he would become sullen, stubborn and irritable. During these episodes he would keep saying that he was in a dream.

On examination his spontaneous complaint was "I'm in a dream. You don't know how awful it is, I get thousands of impressions and they don't mean anything. I'm afraid I don't even know your name." He gave the date as 1960, but could not give the name of the hospital. He gave the dates of the beginning and end of the First World War correctly, but not the second, of which he vaguely recalled that he was farming, and in the Fire Service.

He was able to give the names of all the farms at which he had been, except the present one, where he went four months before the onset of his illness. He gave the reigning monarch as Edward VIII and did not know who was the Prime Minister. He gave accurately the capitals of 7 foreign countries, 5 large towns in England, 5 breeds of pigs and 5 kinds of hen. His performance on the 100–7 test was rapid and accurate. On the Name, Address and Flower test, after *one* minute he recalled only the flower.

Physical examination revealed no abnormal signs, either in the nervous system or elsewhere.

On April 12, 1956, he was seen by Dr. Eliot Slater, who found his manner surly and aggressive. When asked how he was, he replied: "I don't know—you should know better than me." He complained that he was unable to remember anything of what happened, even a few hours previously. He had no idea how long he had been in hospital, saying that it might be a matter of hours or weeks. He said that he was "living thousands of different lives," and that this life (in which he was currently speaking) was only one of them. In a little while he might be talking to someone else and would be told that the present experience was imaginary. It was difficult to get him to provide any details about any of the thousands of lives, some were in the country, some were in houses: he was always with strangers not with people he knew. He did not know whether he himself was always the same, and could not say that he might not sometimes be himself at an earlier age, e.g. a boy. Dr. Eliot Slater considered that the patient might be having eidetic memories of the past, but owing to gross failure of retention was unable to fix them in time, so that they would seem to be recollections of things that had happened a very short while ago.

At a subsequent interview on April 25, Dr. Slater noted that the patient had been visited by his wife that afternoon but had no recollection of this visit. He was told that she had been to see him, but on two subsequent occasions during the interview failed to remember that he had been told this. He recalled being in the Fire Service during the war, but nothing that had happened since the war. He could remember nothing about his three children (aged 11, 8 and $4\frac{1}{2}$). He remembered being married but nothing about the marriage ceremony. It appeared that his retrograde amnesia was solid for eleven years and patchy for about twenty years.

He was examined by Professor Zangwill on March 29, 1956, who reported as follows:

The main features on memory testing are:

(1) Slow and faulty learning, with stereotyped errors.

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(2) Under-estimation of items in a series and of the duration of an interval. Ten repetitions of the Babcock Sentence were said to be four, and an interval lasting 40 seconds was judged to have lasted 5 or 10.

(3) Intact immediate memory span. He can give 7 digits forwards and reproduced the gist of the "cowboy" story more or less adequately from immediate memory, though he could not recall it at all five minutes later.

(4) There is no re-duplicative paramnesia on testing with pictures and objects, but very rapid forgetting and failure to recognize test objects or to recall that he had seen them before.

He does not fabricate, but constantly reiterates that his distant memory is intact, that he feels he is six or eight people, that he is living in a dream, etc. He is quite unaware of repeating himself.

Professor Zangwill concluded that this gross amnesic syndrome, without appreciable intellectual deterioration on formal tests, suggested involvement of the corpora mammillaria and related structures in the diencephalon. All features were consistent with an organic amnesic state and he could detect no hysterical features whatsoever.

An EEG remained similar to the previous records, although there was slightly more low-amplitude theta activity present. There were no reliable lateralizing features present, but the record was considered minimally abnormal.

His third admission to the hospital was on August 27, 1957. In the interval his moods of irritability had become worse, and he was admitted to the Holloway Sanatorium, as a voluntary patient, in November 1956, where he had remained since.

His complaint on this occasion was loss of memory, and depression, and that there were a thousand people occupying his body, which was not his own, and with which he was not free to do as he wished.

Physical examination, as before, was negative.

He knew he was in a hospital, but could not name it. He had no knowledge of having been in it before. He had no idea of the date or month, knew that the year was after 1956, but not which year. Although he was unaware whether he had had lunch, he looked out of the window and correctly deduced that it was afternoon. He was unable to give his home address. He gave his age as 36 (in fact 40). His performance on tests of intellectual function was generally as on the occasion of his last admission, but with evidence of some improvement.

When examined by Professor Zangwill he was able to recall up to 4 out of 5 objects presented visually, each for about 5 seconds, and could recall some of the items for longer intervals. He denied, however, that a drawing of a map of England, which he had done some minutes previously, was his own work.

Professor Zangwill's summary reads as follows:

"There is certainly an organic amnesic syndrome, with severe retention defect for current events and considerable retrograde amnesia for events preceding the onset of the illness. But I think there has been an odd psychopathological reaction to the memory defect, and I suggest that there is now an hysterical or pseudo-demential factor involved in it. His retention defect is not currently as severe as it would superficially appear, and he should be capable of better orientation than he in fact presents. His odd ideas about leading different lives, or changing into other bodies, were (I think) in the first instance simply ways in which he tried to describe to others what it felt like to have a very severe memory defect with 'moment-to-moment' consciousness. But they have now acquired a more primary significance for him, and in some sense he really believes them."

The patient returned to Holloway Sanatorium, where he has remained, his condition being essentially the same in January 1960 as it was two and a half years previously.

Case III

Summary.—A woman, aged 46, in March 1956 had recurrent fever on three occasions, at monthly intervals, the last followed by confusion and delirium. The cerebrospinal fluid showed a pleocytosis, initially polymorphonuclear, but soon lymphocytic, associated with a rapidly increasing protein content. She was left with a retrograde amnesia, which was patchy for thirty years and dense for twenty years. There was a severe defect of recent memory, without corresponding intellectual deficit. Three years later there has been no improvement in her memory.

Mrs. L. H. (No. 74798), aged 46, was admitted to The National Hospital, Queen Square, under the care of Dr. M. J. McArdle, on September 23, 1957.

Her disability, as described by her husband, was impairment of memory and withdrawal of contact with people, including her family.

There was no family history of nervous or mental disorder.

There was no past history of any significant illness, but she had suffered from occasional headaches. Her childhood and adolescence were uneventful. At the age of 24 she married a fisherman, and had a son and daughter. She was a capable, pleasant and sociable person before her illness. At the age of 25 she was awarded a Royal Humane Society Medal for rescuing a child from drowning.

Present illness.—Eighteen months before admission she had a febrile illness without other symptoms, diagnosed as influenza, from which she recovered completely in a few days. A month later she had a similar episode of illness, again with complete recovery. Again a month later she developed fever and malaise without other symptoms, and after two days became confused and delirious, and was admitted to a local hospital.

There were no abnormal physical signs other than drowsiness and delirium. Lumbar punctures, on consecutive days, revealed fluid at normal pressure. There was a marked pleocytosis, which was polymorphonuclear initially, but became lymphocytic. The protein content was high and rapidly increased over the first few days (*see* Table II, 1–3).

TABLE II.—TABLE OF C.S.F. FINDINGS IN CASE III

	Date	*Colour*	*White cell count/c.mm.*	*Poly. %*	*Lymphos. %*	*Protein. mg.%*	*Glob.*	*Lange*
1	5.5.56	Slightly opalescent	245	59	41	90	+	—
2	6.5.56	Slightly turbid	397	2	98	200	—	—
3	?.5.56	Cloudy and faintly yellow	400	0	100	400	+++	
4	6.6.56	Clear				75	—	—
5	?.8.56	Clear	—	—	—	Nearly normal	—	—
6	?.2.57	Clear	9	0	100	65	—	
7	1.10.57	Clear	1	0	100	30	0	33221-00000

She was treated with parenteral penicillin and streptomycin, the provisional diagnosis being tuberculous meningitis, although no organism had been seen, or cultured. After a fortnight her mental state varied from extreme over-activity (jumping up and down on her bed) to complete inaccessibility, and she was transferred to a mental hospital, with a diagnosis of encephalitis. Here she was found

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to be confused, restless and disorientated. She was able to recognize her husband, but not other people. A lumbar puncture done in June (*see* Table II, 4) showed that the cerebrospinal fluid was now normal except for a slightly raised protein content. She had persistent anorexia with occasional vomiting and had to be coaxed to eat. Later her restlessness disappeared, and she became apathetic. Conversation was no longer spontaneous; she sat in silence when her husband visited her and would reply to any question with "I don't know."

In September 1956 she was given a course of E.C.T. as she was considered to have an atypical depressive reaction following a post-encephalitic confusional state. This was not followed by improvement, and in January 1957 she was discharged home. She spent most of the time in bed and would get up and dress with reluctance and irritability. She would comply with suggestions such as making the bed, cooking a meal, washing the dishes, but remained sitting in a chair at other times. At first she did not recognize her own home and would have to look in a cupboard to see where to put the china away. She improved in this respect, and was able to knit, read music and play the piano from a score. In February 1957 she began vomiting again and was admitted to hospital, where she lay quiet and unco-operative. Lumbar puncture at this time revealed a fluid with a slightly raised protein and lymphocyte count (*see* Table II, 6). The vomiting stopped, but her mental condition remained the same as before her admission.

In September 1957 she was admitted to the National Hospital, where no abnormal physical signs were found. She sat with one hand covering her face, replying in a barely audible voice. She was unable to find her bed in the ward. She knew her name and address, that she was married and had children. When asked the year of her birth she replied "1900," when she was in fact born in 1910. She did not know the date and thought it was 1940. She knew she was in hospital, but did not know where it was situated (even whether it was in Cornwall). She remembered her father was a tailor, knew she was the youngest in the family, and correctly listed her brothers' and sisters' names.

She knew which school she had attended and described the job and employer she had on leaving school. She could now remember winning the Royal Humane Society's Medal (in 1935). She was able to give the names of her two children, but not their respective ages, nor their jobs. She did not know whether her parents were alive (they had died four years previously) or whether her employer was alive (he had died six years previously). She knew of the First World War, but not of the second. She remembered King George V was on the throne when she was a child, but did not know if he was still alive. She was able to retain 6 digits forwards, and 4 digits backwards. She could do the serial 7 test with difficulty and persuasion, but then making several mistakes. She tried only once to repeat the Babcock sentence and was inaccurate. She was extremely poor at simple arithmetic and gave wrong answers to 6 multiplied by 4. She was unable to retain a name, address, and the name of a flower, one minute after being told.

On October 9, 1957, 0·2 gramme amylobarbitone sodium was injected intravenously. This relieved the overlying aggression and made her more amenable to questioning. No improvement in recent memory was evident, but she elaborated much more on details of her early life. During the Amytal interview she admitted that her memory had gone and that she felt lost.

She was seen by Dr. R. Pratt, who reported: "I found that this patient was not able to retain 'new' information (e.g. that she was in London) for more than a minute. Her retrograde amnesia and her defect of retention suggests that the disease process severely affected the base of the brain. Of great psychiatric interest is her anxious mental attitude in that when given questions she cannot answer she will ignore them, or, if pressed, say 'I don't know.' She denied depression. There was no con-

fabulation at all—in fact, the complete reverse of this. I would regard her attitude as being a form of catastrophic reaction to her organic memory impairment."

She was seen by the psychologist (Mrs. M. Wyke), who found her unco-operative and negativistic. Although she wrote her name she was unable to recognize it two minutes later as her own signature. It was considered that, although the precise degree of intellectual impairment was difficult to establish, it was not comparable to the severe degree of memory loss.

Investigations, including hæmoglobin, white cell count, sedimentation rate, W.R. in blood and C.S.F. were all normal, as was examination of the urine and an EEG.

X-rays of the chest and skull were normal, but an air encephalogram showed dilated lateral ventricles, left more than right, with well-marked focal dilatation of the temporal horns, particularly at their anterior ends, and particularly that on the left side: there was very little filling of the subarachnoid cortical channels, although an attempt was made to inject air into these via the basal cisterns.

The cerebrospinal fluid was normal except for a mildly paretic Lange curve (Table II, 7).

In December 1959 she was reported to be in a mental hospital and to show no improvement in memory.

The evidence for the diagnosis of encephalitis in the next case is incomplete. The cerebrospinal fluid was not examined in the early stage of the illness. Moreover the later story is complicated by recurrent epileptic seizures. Nevertheless the patient's mental state when last examined more than two years after the onset resembles so closely that of the 3 patients already described that the case is included in the series.

Case IV

Summary.—A man, aged 29, while under treatment for pulmonary tuberculosis developed a febrile illness with confusion A month after the onset he had a series of epileptic seizures. He recovered from the confusion, but was left with a retrograde amnesia, which was practically complete for three years before his illness, and a severe defect of recent memory. These symptoms showed a little improvement two and a half years after the onset of the illness. There was little, if any, intellectual loss in fields other than memory. Knowledge and skills ante-dating the retrograde amnesia were preserved. He continued to have an occasional epileptic seizure.

G. H., aged 30, was admitted to the National Hospital, Queen Square, under the care of Sir Charles Symonds on September 26, 1948. His complaint was of loss of memory for recent events and mistiness of vision in the right eye.

There was no family history of mental or nervous disorder.

At school he was above average at work and games. On leaving school he was first apprenticed to a painter, but after eighteen months he gave this up to join the Merchant Navy, joining the Royal Navy in 1936. On the outbreak of war he volunteered for submarine service, in which he continued on active operations until the end of the war, rising to the rank of Stoker Petty Officer and being awarded the *D.S.M.* He was married with two children. There was no history of alcoholic excess.

In January 1947 he was found to have pulmonary tuberculosis and admitted to an appropriate hospital, where he had a phrenic avulsion and artificial pneumothorax. He was finally discharged home in November 1947, having been invalided from the Service.

Present illness.—His wife states that when he arrived home he had a severe cold and raised temperature. He was put to bed and attended by his local doctor. He complained that his eyes ached but had no other symptoms, though he was unusually drowsy. A week after his return home his wife noticed that he was forgetful, often telling her to do things about their new house which she had already told him she had done. Three weeks after the onset of the illness he was sent by ambulance to

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the local hospital for a refill of his pneumothorax and returned the same day none the worse. Within the next forty-eight hours, however, he had become confused and during the subsequent week was delirious and apparently hallucinated. At the end of this week (about a month after the onset of his illness) he had a series of seven or eight generalized epileptic seizures in the course of two hours, and was admitted to the local hospital, where he remained until January 1948. On his return home his wife found him silly in his conversation and unclean in his habits for the first month. There was subsequent improvement in this respect. In May his right eye became bloodshot and had a film over it, and he complained of loss of vision in this eye. A week later he had a single epileptic seizure, and a similar attack in August.

On examination no abnormal physical signs were detected except for lenticular opacities in the right eye. There was no dysphasia or dyspraxia. His behaviour was not abnormal, He was greatly distressed by the defect of memory, which was his main complaint. He could recall nothing of his illness or of the events preceding it for about three years (with a few islands of uncertain memory). The routine tests of intellectual function showed that he could retain 6 digits. He did the serial 7 subtraction test correctly in average time, and was up to normal standards in mental arithmetic. His general knowledge for past events was good, but his knowledge of current events extremely scanty. With the Name, Address and Flower test he was unable to recall any item after five minutes.

Radiograms showed no abnormality in the skull and evidence of quiescent pulmonary tuberculosis in the upper lobe of the right lung. He discharged himself from hospital before further psychological investigations could be carried out.

He was readmitted on March 20, 1950. His complaint then was of his defective memory. This defect he stated was in remembering day-to-day happenings. When asked how long he had been ill he replied that to him it was as if it had just started and that he came out of the Navy yesterday and all that had happened in the interval was a blank.

Interval history.—His wife stated that since he was last in the National Hospital his memory for recent events had not improved. His memory for the remote past appeared to her to be normal, but he appeared to have no memory of his illness and had very little recollection of day-to-day events. He had had a recurrence of the epileptic seizures about once every four months, always occurring in the early morning. Her description was that of generalized convulsion, occasionally with incontinence of urine. The duration of the attack was a few minutes. He would then go off to sleep again and be unaware when he next woke that he had had an attack. He was generally less patient and more irritable than before his illness, but clean and tidy in his habits. He took an interest in golf and did the *Daily Express* crossword puzzle daily, often completing it.

On examination his physical state was as previously recorded. His retrograde amnesia was little altered. He gave a consecutive account of his past life up to the end of his service in the Navy, though he did not remember the circumstances of his leaving it or the fact that this was due to his chest trouble. Of subsequent happenings he had only occasional isolated and vague recollections.

He was correctly orientated for time and place, but could give no account of what had occurred on the previous day (though he had travelled up from Kent to come into hospital). Formal tests showed that he retained 7 digits forwards and 6 backwards. He reproduced the Babcock sentence correctly at the sixth attempt. He completed the serial 7 subtraction text correctly in 20 seconds. He made no errors in mental arithmetic. *He recalled no item in the Name, Address and Flower test after five minutes.* His general knowledge in so far as this had been acquired before the time of his amnesia was that of a person of above average intelligence.

He was examined by Professor Zangwill on April 19, 1950, who observed: "This patient shows the picture of a diffuse and somewhat fluctuating amnesia for recent events; this is associated with grossly impaired learning and retention tests. As is usual in these cases, however, immediate memory (as tested by digit span, etc.) is intact. There is very little intellectual loss in fields other than memory. The amnesic syndrome is clearly of organic type and the lack of intellectual defects in other spheres suggests that it may have a subcortical basis. In my opinion there is no evidence of emotional (i.e. psychogenic or reactive factors) complicating the organic memory defect, but there is probably some degree of personality change of the kind often found in Korsakoff states."

Lumbar puncture yielded a clear and colourless cerebrospinal fluid under a pressure of 110 mm., containing no cells and 60 mg. per cent of protein. There was no excess of globulin and the Lange was unchanged. The Wassermann reaction was negative in blood and cerebrospinal fluid. Examination of the blood showed no abnormalities. An air encephalogram showed good filling of the ventricular system, which was normal in size, shape and position. The EEG showed a symmetrical alpha rhythm unchanged by over-breathing, with no other significant activity.

Discussion

In each of the 4 cases described the end-result of the illness was very much the same, the distinctive features being a retrograde amnesia for several years before the onset of the illness, and a severe defect of recent memory with relatively little impairment of other intellectual functions. In each case at the onset of the illness there was fever and confusion, and in the three instances in which the cerebrospinal fluid was examined a significant pleocytosis was observed, and in 2 of these cases a paretic Lange curve was found. It may therefore be fairly assumed that the illness was an infection of the central nervous system, in the course of which there occurred irreparable cerebral damage. The questions now to be discussed are whether there are any clues either to the nature of the infection, or the localization of the lesions.

We have not been able to discover any particular variety of encephalitis or meningo-encephalitis having the pattern observed in our cases, in which during the acute phase there appears to have been no clinical evidence of meningitis or focal cerebral lesions. The findings in the cerebrospinal fluids would be consistent with a viral encephalitis with an unusually protracted course, but we can go no farther than to suggest that the disease was of this nature. The question of its localization lends itself to more extensive consideration, having regard to the observation of the striking combination of retrograde amnesia and defect of recent memory in other conditions in which the site of cerebral damage is known or may be reasonably presumed.

In the past few years there have been several reports of memory defect following temporal lobectomy. Scoville (1954) reported that bilateral resection of the temporal lobe in man resulted in no marked physiologic or behavioural changes with the one exception of a very grave recent

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memory loss. Milner and Penfield (1955) recorded 2 cases in which resection of the dominant (left) temporal lobe was performed for epilepsy, including the uncus, amygdala and hippocampal zone. Psychometry before and after operation showed no post-operative impairment of intellectual function as a whole, the pre- and post-operative I.Q. being approximately the same. There was, however, a marked contrast between the patients' excellent achievement on tests of attention and concentration, such as digit retention and mental arithmetic, and their inability to recall test material after a lapse of as little as five minutes. The loss was a general one, affecting new learning of stories, drawings and numerical material, but leaving previous knowledge relatively intact. Recognition was impaired as well as recall. Both these men were able to earn their living following operation, one as a glove cutter and the other as a draughtsman. The authors' conclusion was that there was pre-operatively in each of these cases an unsuspected, but more or less completely destructive, lesion of the right hippocampal zone.

Scoville and Milner (1957) reported 8 cases of memory defect following bilateral temporal lobectomy. In 7 of these the operation was performed in the hope of alleviating a psychosis of long standing. The remaining patient, a man aged 29, had had epileptic seizures since the age of 16 which were completely disabling despite full medication. On recovery from the operation the patient gave the date as March 1953 instead of April 1955, and his age as 27 instead of 29. There was a partial retrograde amnesia for three years. Psychometry revealed a striking contrast between his good general intelligence and his defective memory. On the Wechsler-Bellevue Intelligence Scale he achieved a full I.Q. rating of 112 as compared with a pre-operative rating of 104. On the Wechsler Memory Scale his rating was 67 and he failed to improve with repeated practice. On all tests it was found that once he had turned to a new task the nature of the preceding one could no longer be recalled, nor the test recognized if repeated. Formal testing in the psychotic patients of the series was hindered in most instances by lack of co-operation, but there were two in whom psychometry two years after the operation revealed a gross defect of recent memory. One of these patients achieved a Wechsler I.Q. rating of 122 but was unable to learn either the name of the hospital or the examiner, though told them repeatedly. Each time he received the information as something new and a moment later would deny having heard it. At the examiner's request he drew a dog and an elephant, yet half an hour later he did not recognize them as his own drawings.

In the remaining 5 cases the memory defect was of moderately severe degree. Correlation of the extent of lobectomy, which varied in different cases, and the degree of memory loss, led the authors to conclude that

all patients who had had medial temporal lobe resections extensive enough to damage portions of the hippocampus and hippocampal gyrus bilaterally showed a persistent disturbance of recent memory which was most severe in the two most radical excisions, in which the posterior limit of removal was at least 8 cm. from the temporal tips. They comment on the important anatomical connexions between the hippocampus and the mammillary bodies and the reported occurrence of a specific defect of recent memory with lesions of the latter structures.

Walker (1957) presented a study of 3 cases of unilateral temporal lobectomy followed by memory loss. In the first case the onset was delayed, and it is doubtful whether the memory defect was a direct result of the operation, which was undertaken in the hope of relieving epileptic seizures. The second patient, also operated on for temporal lobe seizures, showed a severe post-operative defect of recent memory, but refused to co-operate in mental testing. The patient returned to the management of a large store, so that the defect appears to have been temporary. In the third case, in which a left temporal lobectomy was performed for epilepsy, there was post-operative confusion and when this cleared a retrograde amnesia for about five years, and severe defect of memory for recent events. This was found to have persisted three years after the operation.

A condition resembling that described in our cases may also be observed as a transient phenomenon after a closed head injury. Russell (1935) has described a characteristic example. His patient was aged 22 and sustained his injury in August 1933. A week after the accident he was able to converse sensibly, and the nursing staff regarded his mental state as normal. When questioned, however, he said that the date was February 1922, and that he was a schoolboy. He had no recollection of five years spent in Australia and two years in this country working on a golf course. Three weeks after the injury he returned to the village where he had been working for two years. He had no recollection of ever having been there before and lost his way on more than one occasion. He was able to do his work, but had difficulty in remembering what he had actually done during the day. The retrograde amnesia gradually shrank, and he was finally able to remember everything up to within a few minutes of the accident.

Comparable cases have been recorded by Symonds (1937). The usual sequence is that of traumatic stupor followed by confusion, and thereafter by a condition closely resembling Korsakoff's psychosis, in which there is a gross defect of recent memory with relative preservation of other intellectual functions. This is associated with a prolonged retrograde amnesia, which shrinks, with recovery of the current memory defect. Having regard to the frequency with which bilateral contusion of the temporal poles is found in fatal cases of closed head injury it

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seems not unreasonable to suppose that the traumatic Korsakoff syndrome is dependent on lesions in this situation.

Korsakoff (1889) in his last paper concerning the psychosis which bears his name emphasized the contrast between the gross defect of recent memory and preservation of other intellectual functions. "The patient," he says, "gives the impression of a person in complete possession of his faculties; he reasons about everything perfectly well, draws correct deductions from given premises, . . . plays chess or a game of cards, in a word comports himself as a mentally sound person, . . . He forgets what happened to him just an instant ago; you came in, conversed with him, and stepped out for one minute, then you come in again and the patient has absolutely no recollection that you had already been with him." Korsakoff also stressed the fact that the patient's memory for events long before the illness was usually unimpaired, though in some cases there might be retrograde amnesia. The retrograde amnesia in Korsakoff's psychosis of alcoholic origin may be as long as ten years (Zangwill, 1960). There is, however, in Korsakoff's psychosis more general impairment of intellectual function, less insight, and a greater tendency to confabulation than in our cases. It is now generally considered that the basis of Korsakoff's psychosis is the pathological condition known as Wernicke's Encephalopathy (Victor and Adams, 1953), (Malamud and Skillicorn, 1956), in which there are lesions comprising foci of vascular stasis and parenchymatous degeneration, occurring symmetrically in the corpora mammillaria, and also, though not constantly, in other parts of the hypothalamus, the fornix, the juxtaventricular zone of the thalamus, the peri-aqueductal grey matter of the mid-brain, the posterior colliculi and the floor of the fourth ventricle (Campbell and Biggart, 1939).

Williams and Pennybacker (1954) reported 4 cases in which there was a well-defined defect of memory associated with tumours (craniopharyngioma) involving the floor and sides of the third ventricle. In all these cases the immediate memory span was normal, but recent memory was severely impaired with a tendency to confabulation. There was also some general impairment of intellectual function, and deterioration of personality, the clinical picture therefore resembling that of Korsakoff's psychosis. From their analysis of this and other material these authors concluded that memory impairment in cases of brain tumour is most common and specific when the floor and walls of the third ventricle are damaged.

Ajuriaguerra, Hécaen and Sadoun (1954) have recorded comparable disturbance of memory in cases of tumour involving the hypothalamic structures and have fully reviewed the literature of this subject. They conclude that tumours causing a Korsakoff syndrome are very frequently but not invariably, found to involve the corpora mammillaria. They

relate the syndrome to lesions either of the anterior part of the hypothalmus or the walls of the third ventricle.

Sweet and others (1959) have recently reported the case of a woman aged 36 in whom the operative removal of a large colloid cyst of the third ventricle required section of the anterior columns of the fornix. Following the operation there was a retrograde amnesia complete for at least several weeks and patchy for four or five years. At first there was loss of skills previously acquired. She had, for example, forgotten how to use a knife and fork. These were rapidly recovered. The outstanding symptom, however, was a severe loss of memory for recent events, which together with the retrograde amnesia was still present two years after the operation. In general, memory for remoter events was intact. The authors note that the fornix represents the main efferent projection from the hippocampus to the mammillary body and conclude that the hippocampal-fornix-mammillary body system is a necessary participant in the central process which makes an experience accessible to recall.

We may conclude that in the cases we have described some or all of these structures were involved. In favour of a temporal lobe localization is the occurrence of epileptic seizures in 3 of the 4 cases, and the focal dilatation of the temporal horns shown in the air encephalogram of Case III.

Summary

Four cases are reported of an illness beginning with fever and delirium in which after recovery from the acute phase the patient was left with permanent intellectual impairment.

In the 3 cases in which the cerebrospinal fluid was examined there was an increase of cells and protein during the acute phase of the illness.

In 3 cases epileptic seizures occurred during the early stage of the illness.

In all 4 cases there remained as permanent effects of the illness a retrograde amnesia of two or more years, and a gross defect of recent memory with relatively little impairment of other intellectual functions.

The nature of the illness and localization of the lesions are discussed, with the conclusions that it was a viral encephalitis, with a selective incidence upon the hippocampus, fornix or mammillary bodies, the most probable site being the anterior part of the temporal lobes.

Our acknowledgments are due to Dr. E. A. Carmichael and Dr. M. J. McArdle for permission to refer to the cases under their care; to Dr, Eliot Slater and Professor Zangwill for leave to quote their observations. and to the latter for his help and advice in the preparation of this paper.

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ELECTROPHYSIOLOGICAL ANALYSIS OF A CASE OF TAY-SACHS DISEASE

BY

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THERE have been several reports of electroencephalographic findings in infantile Tay-Sachs disease (Rohmer, Israel and Wackenheim, 1954; Bjelkhagen, 1950; Rosenbaum and Stein, 1953). In addition Watson and Denny-Brown (1950, 1953, 1955) have presented detailed clinical and electrophysiological correlation studies in a patient with myoclonus epilepsy in whom the presumptive diagnosis was juvenile amaurotic family idiocy. However, none of the previous observations have been concerned with long term changes in the pattern of electrogenesis as the disease progresses. In the case to be reported here the opportunity was presented for long term study of alterations in spontaneous electrogenesis and in responses to stimulation as greater and greater cerebral degeneration took place. The pattern suggested significant differences in the response of various sections of the central nervous system to stimuli applied at various stages of the disease.

CLINICAL HISTORY

The patient was 9½ months old on admission to hospital in April 1953. There was a history of normal full-term delivery and apparently normal development up to the age of 6 months. At that time the patient's mother noted that the child did not roll over by itself, did not maintain posture when held in a sitting position and was extremely hypersensitive to sounds. Even slight noise caused a startle reaction.

Family history revealed no evidence of nervous or mental disorder. There was one brother 3½ years old who was quite normal in all respects.

Physical examination on admission revealed a child who lay unresponsive except when startled by sudden noise. The latter would invariably be followed by a marked Moro reflex which was excessive in degree but brief in duration, i.e. was a unitary event, a single response to stimulus. The child did not smile and cried intermittently without apparent precipitation by outside events. When left alone she lay fairly still with a vacant stare. All limbs could be voluntarily moved, but there was general

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hypotonia. The patient reacted to light flashed into the eyes and followed moving objects around the room. Pupillary responses were intact. The optic fundi appeared atrophic, the retinæ were pale with a smooth, shiny texture. There was a "cherry red" spot in the macula. Other cranial nerves were intact. The child responded to pin-prick and light touch on all skin areas but more detailed sensory examination was of course impossible. The tendon reflexes were active and symmetrical. A Babinski sign was present bilaterally, but there was no Hoffmann, no grasp reflex, and no tonic neck reflex. The general physical examination was normal except for coryza and a mild conjunctivitis. There were no seizures.

The physical signs remained essentially unchanged for approximately six months. However, toward the end of October 1953 some hypertonicity of the lower extremities was noted and at rest the legs were extended and arms held flexed in the classical posture of decortication. The exaggerated response to noise was still present but had changed in character. A loud clap or adventitious noise resulted in a violent jerk and sudden extension of all limbs with arching of the back and neck muscles. Occasionally a tonic seizure lasting 30–40 seconds would result.

By December of 1953, eight months after admission, all reflexes were hyperactive, tonic neck and body righting reflexes were present and extensor spasms of all extremities could be elicited by traction on the limb musculature. An active grasp reflex was present and there was no sucking reflex. The eyes still followed bright light and pupillary reactions were intact.

In March and April 1954, one year after admission, the patient began to have spontaneous myclonic twitches sometimes generalized and bilaterally synchronous and sometimes limited to one or another extremity. At this time the eyes no longer followed objects about the room but blinking occurred in response to a finger approaching the eye.

During the succeeding eight months the child gradually deteriorated. Myoclonic seizures became more and more frequent and could be triggered by any sensory stimulation. Pupillary reactions to light and blinking to threat disappeared. There were fine spontaneous irregular movements of all limbs. All limbs were spastic and the tendon reflexes were hyperactive throughout. The child lingered on until October 1955, having repeated bouts of pneumonia with spiking fever. She finally died during one of these intercurrent infections.

The pathologic data will be reported elsewhere, but it should be stated here that the microscopic findings show the characteristic lipoid inclusions of cerebromacular degeneration. Lesions were present throughout the neuraxis but were most prominent in cerebellum, brain-stem, thalamus, basal ganglia and occipital lobes.

Results

The clinical course of the patient could be divided into four fairly distinct stages.

Stage I.—Musculature was generally hypotonic. Pupils reacted to light and eyes followed a moving object around the room. The Babinski sign was present bilaterally; there was no Hoffmann, no grasp reflex, no tonic neck reflex. There were no seizures. The child responded to auditory stimulation with a brief, violent jump with flexion of all extremities.

Stage II (approximately eight months after admission).—Stage II was signalled by the development of hypertonicity first noticed in the extensors of the lower extremities and then in the flexors of the upper extremities.

All tendon reflexes became hyperactive. At rest with the child on its back the legs were extended and the arms held adducted and flexed in the classical posture of decortication. Tonic neck and body righting reflexes were present and extensor spasms of all extremities could be elicited by traction on the limb musculature. There was an active grasp reflex and the eyes still followed moving objects. A loud noise now evoked violent extension of all limbs (rather than flexion) with arching of back and neck muscles. Occasionally a tonic seizure lasting 30–40 seconds would result.

Stage III (about one year after admission).—This stage began with the development of spontaneous myoclonic twitches, sometimes generalized and bilaterally synchronous, sometimes limited to one or another extremity. Myoclonic seizures could be triggered by sensory stimulation of any sort, i.e. light, sound, pin-prick, tendon tap, etc. The eyes no longer followed objects around the room but blinking occurred in response to a finger approaching the eye.

Stage IV (eighteen months after admission).—Frequent seizures triggered by any stimulus appeared at this time. There was complete blindness and loss of pupillary response to light. There were spontaneous irregular movements of all limbs. Tendon reflexes were hyperactive throughout.

Electroencephalographic changes may be divided into the following categories:

Resting rhythms.—During Stage I of the clinical course, a resting-waking EEG revealed a wide mixture of frequencies. There were bursts of high voltage slow waves separated by relative silence (fig. 1A) or by lower voltage faster rhythms (fig. 1B). The periodic burst potentials were similar to those described by Cobb, Martin and Pampiglione (1952) in cerebral lipoidosis. In addition a right anterior temporal spike focus was noted early in the disease (fig. 2) which was unassociated with clinical seizures. Succeeding stages (Stage II, fig. 3A; Stage III, fig. 3B; Stage IV, fig. 3C) were characterized by progressive slowing and gradual diminution in voltage of the electroencephalogram. In Stage II, the mixed frequencies seen in the previous figures had disappeared to be replaced by a virtually continuous high voltage slow (1–2 per sec.) spike-wave pattern which was bilaterally synchronous. During this period repeated examinations failed to reveal the previously noted anterior temporal spike almost as though the widely dominant bilaterally synchronous rhythms were utilizing the cortical neurones which had previously responded with the focal spike discharge. In Stages III and IV the bilateral spike-wave was completely gone and the bilateral synchrony of the record also disappeared leaving finally a relatively flat record with occasional rhythms appearing independently in all areas.

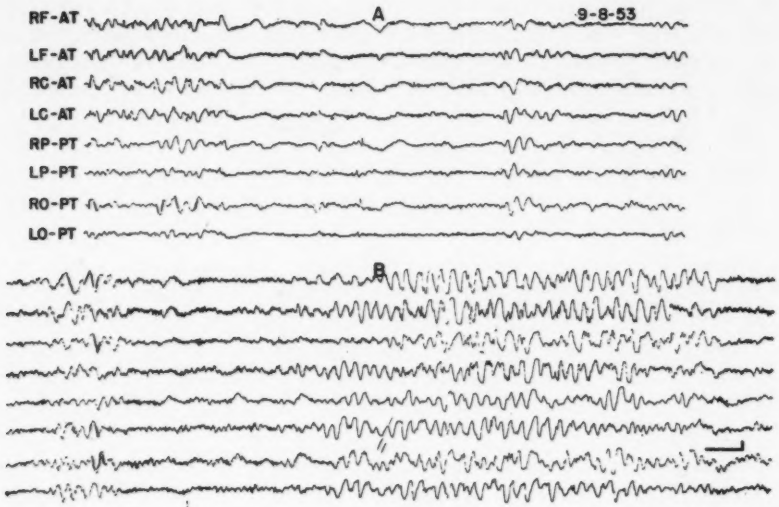

FIG. 1.—Electroencephalogram in the resting-waking state of Stage I. There is a wide mixture of frequencies with bursts of high voltage slow waves separated by relative silence (A) or by low voltage faster rhythms (B). Channel designations are indicated by initials throughout, e.g. RF–AT means Right frontal–Anterior temporal. Calibration is 50 microvolts and one second and is the same for all succeeding figures.

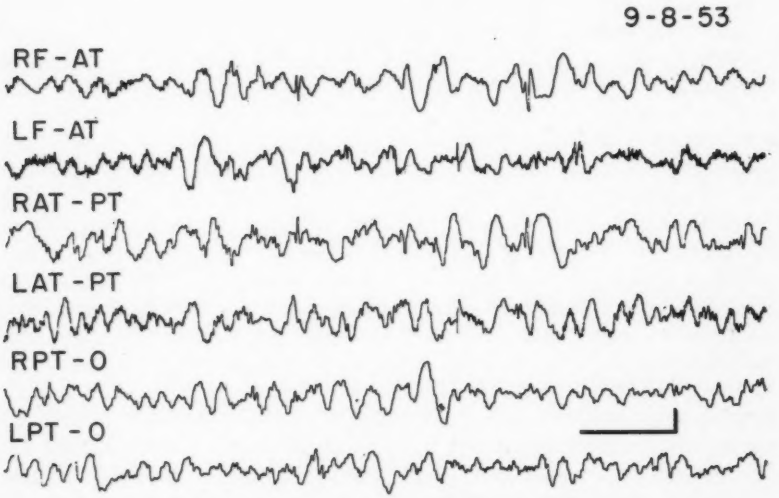

FIG. 2.—Right anterior temporal spike focus in Stage I.

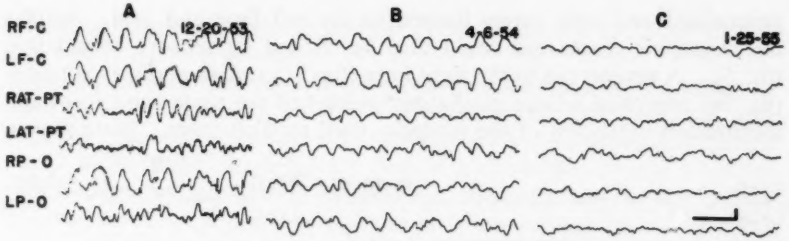

FIG. 3.—Spontaneous electroencephalograms during Stage II (A), Stage III (B), and Stage IV (C).

The resting record of Stage III was occasionally interrupted by a spontaneous seizure discharge which was well localized to the right temporal and occipital region (fig. 4). The discharge was often accompanied by clinical seizures of the myoclonic type which were usually

FIG. 4.—Spontaneous focal spike discharge in Stage III.

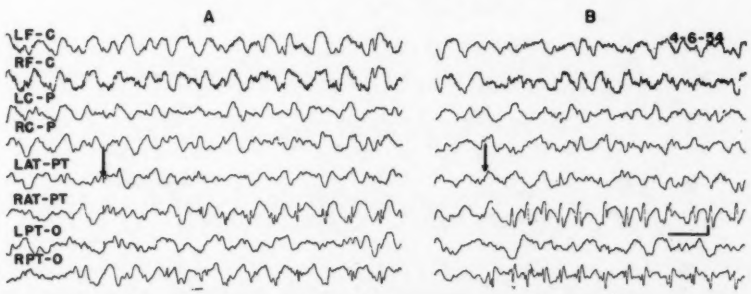

FIG. 5.—Focal discharges elicited by sensory stimulation during Stage III. The arrows indicate a tendon tap to the right knee (A) and an auditory stimulus (B).

generalized and only rarely limited to the left face and arm. Similar electrographic discharges could also be elicited by sensory stimulation (fig. 5). A tendon tap to the right knee (fig. 5A) and an auditory stimulus (fig. 5B) provoked seizure discharges which had the same wave form and localization regardless of the modality used to elicit them. Note that in

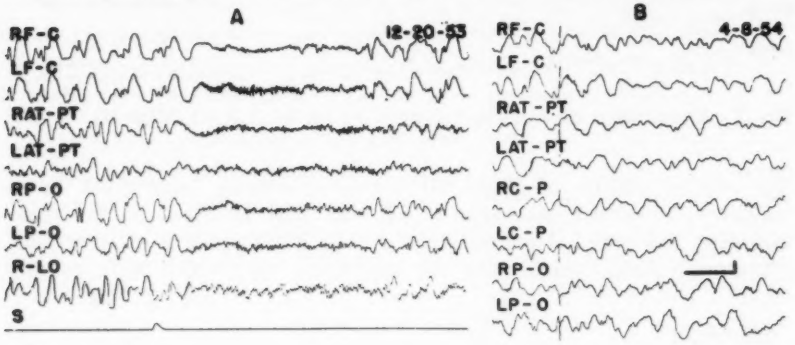

FIG. 6.—Arousal response to sensory stimulation during Stage II (A) and Stage III (B). The stimulus was a touch to the right leg indicated by the deflection on the signal channel in A and by the stimulus artifact seen in all channels in B.

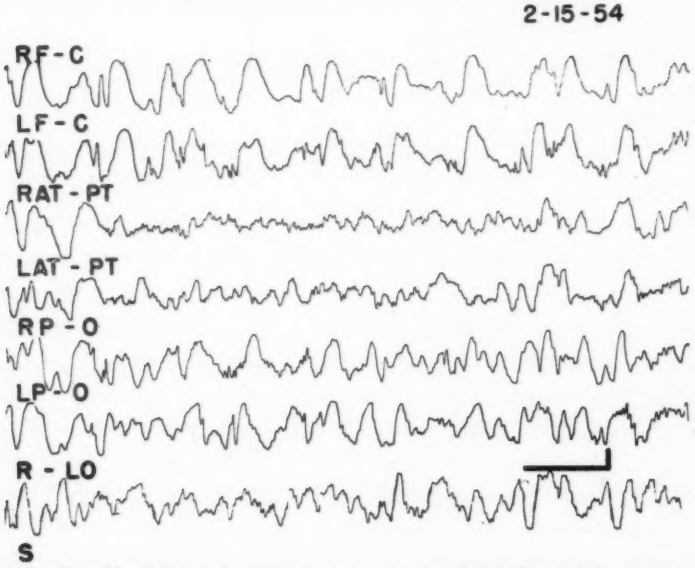

FIG. 7.—Localized arousal response to sensory stimulation when patient was in transition between Stage II and Stage III. The stimulus is indicated by the black line on the signal channel.

this stage there is no evident cortical evoked potential to these stimuli. This will be referred to later.

Arousal response to stimulation.—Fig. 6 demonstrates the effect of touch to the right leg on the EEG of Stage II (fig. 6A) compared with Stage III (fig. 6B). In Stage II a clear-cut arousal or activation pattern is seen in all leads. In Stage III there is no electrical change whatever even though the stimulation produced a peripheral myoclonus. Such changes however did not take place in an all-or-none fashion. The loss of the arousal response was gradual but, perhaps more important, did not occur in all brain areas at the same time. Fig. 7 represents a record taken in February 1954, when the patient was clinically in transition between Stages II and III, that is between A and B of the last figure. The arousal response to a tone stimulus (black line) was almost gone but persisted in the temporal leads bilaterally. In our patient the temporal areas contained fast rhythms longer than the other areas and seemed the last regions to deteriorate.

Evoked potentials.—Evoked potentials in the appropriate sensory receiving area were recorded in response to tactile, auditory and visual stimuli. The form and latency of these potentials have been observed and well described by Watson and Denny-Brown (1955) and by Dawson (1950) and were confirmed in detail in our study. The electrical response to a tendon tap on the right knee was characterized by a tri-phasic sharp

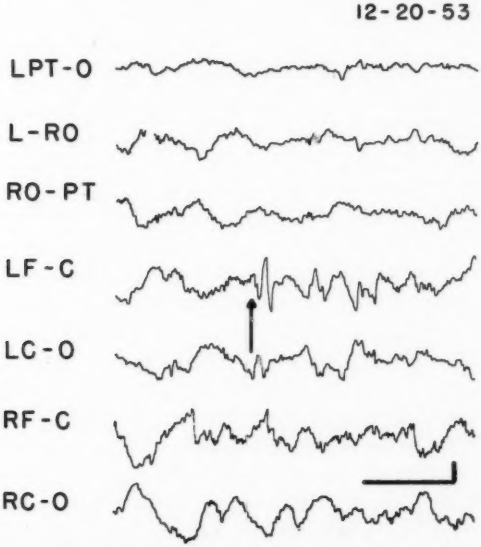

FIG. 8.—Evoked potential recorded in left central derivations in response to a tendon tap on the right knee (arrow). Such responses were observed during Stages I and II.

wave well localized to the appropriate central derivations followed by one or more slow waves which were less well localized (fig. 8).

Watson and Denny-Brown (1950, 1955) noted that the slow component of the evoked potential had a wider surface distribution than the initial di- or tri-phasic deflection. We made the same observation (fig. 9) but

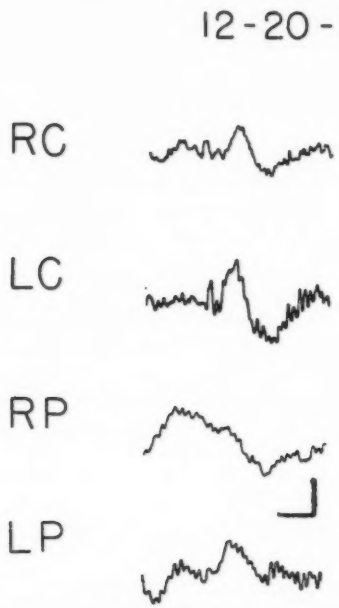

FIG. 9.—Monopolar recording of evoked potential in Stage II. The slow component has a much wider surface distribution than does the primary spike elicited by tendon tap to the right knee. The reference electrode was on the nasion.

also noted that distribution of the slow component was wider in Stage II than in Stage I and that when a response was elicited in Stage III the slow component was again less prominent. Such findings might indicate fairly fundamental differences in neural organization for each stage.

Definite evoked potentials were observed, however, only during Stages I and II. In Stage III a simple evoked potential could not be obtained, but if the tendon tap, for example, was given during photic stimulation a clear evoked potential in the contralateral somato-sensory region appeared (fig. 10). Such facilitatory effect was obtained even when the photic stimulus did not produce a direct occipital driving response by itself, suggesting that the facilitation took place in subcortical circuits. In Stage IV such facilitation was ineffective and no stimulus produced any

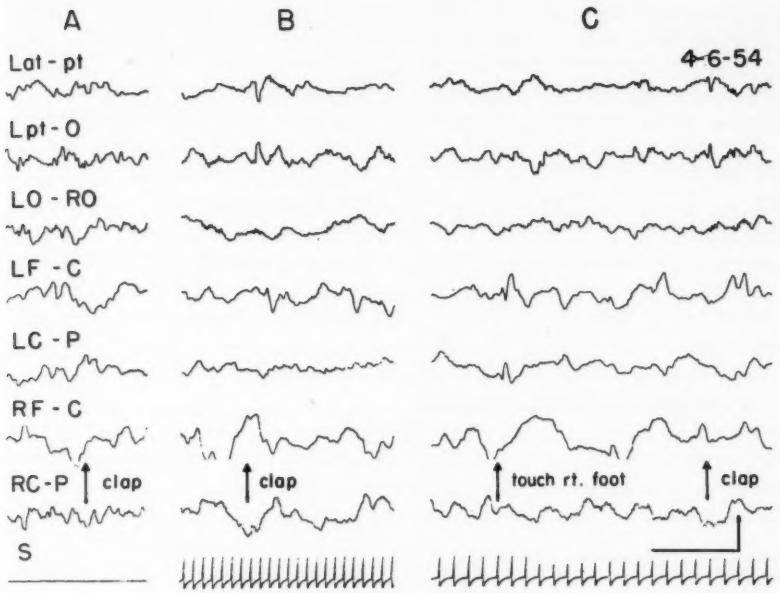

FIG. 10.—Facilitation of evoked potentials by photic stimulation during Stage III. An auditory signal (clap designated by arrow) did not evoke a response in auditory receiving areas when administered without photic stimulation (A). Clear responses were observed in the auditory regions when the acoustic signal was combined with simultaneous photic stimulation (B). Photic stimulation also facilitated a response to a touch to the right foot (C). The specificity of these evoked potentials is clearly indicated by the separate localization of the responses to touch and to a clap (C).

change in cortical rhythms despite the fact that the same stimulus induced a clinical myoclonus.

Responses to photic stimulation.—Initially (Stage I) responses could be obtained in the occipital regions to light flashes ranging from 3 to 12 per second. In Stage III there was an abrupt shift in the spectrum of response. Flicker frequencies at 3 to 4·5 per second elicited a response which began at about 3 per second but soon dropped to 1·5 per second and continued at that rate (fig. 11). Flicker frequencies below 3 or above 5 elicited no response at all. During the same recording a spectrum of stimulus frequencies was imposed running from slow to fast or fast to slow. Responses came in and then disappeared again as one crossed the 3 to 4·5 per second band as though at this frequency a resonating system was entered which triggered or locked into a natural periodicity of the neurons (fig. 11). This too disappeared and in Stage IV no responses could be elicited at any flicker frequency.

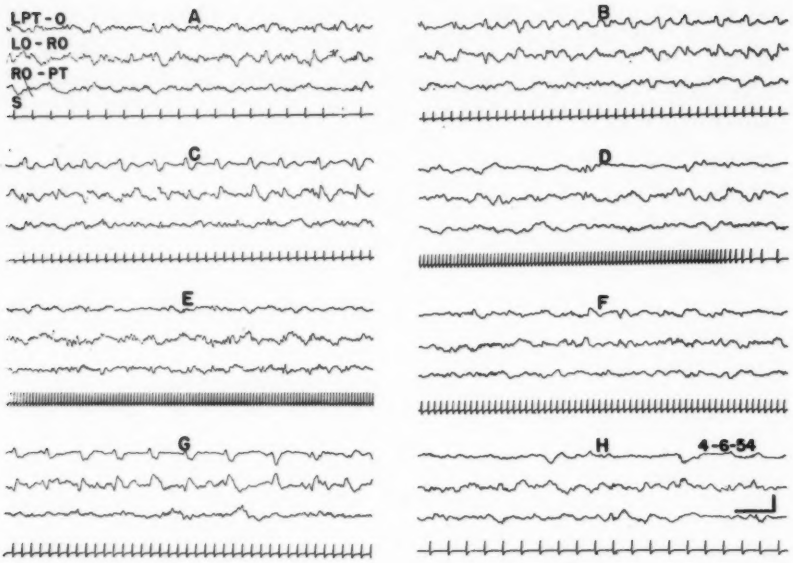

FIG. 11.—Responses to photic stimulation within a limited frequency band. Records are taken from a continuous sequence in which the frequency of photic stimulation was gradually increased from 2·5 per second (A) to 4·5 per second (B and C), 10 per second (D), 12 per second (E), 6 per second (F), 4·5 per second (G), and 2·5 per second (H). These records reveal a peculiar "locking in" of photic responses around the frequency band of 4·5 per second. The responses are rhythmic but are usually slower than the driving frequency. The submultiple response is not constant but varies (compare B and C with record G). In addition it should be noted that the responses appear only in the left occipital derivations and not on the right. It may be recalled that the right occipital region had been involved in focal seizure discharges during Stage III of the patient's disease.

DISCUSSION

One can outline the clinical and electrographic findings as follows. The first stage was characterized clinically by hypotonia, intact vision and absence of seizures and electrographically by mixed fast and slow rhythms, periodic bursts, a right temporal spike focus, good desynchronizing or activating response, clear evoked potentials to sensory stimuli although the latter stimuli did not produce after-discharge or electrographic seizures.

In the second stage vision was still intact but hypotonia had been replaced by spasticity with extensor spasms and the appearance of a proximal traction response, tonic neck and body righting reflexes, grasp reflex and tonic seizures. Electrographically the mixed rhythms were replaced by almost continuous bilaterally synchronous 1 to 2 per second

spike and wave pattern occupying the entire cortex. The temporal focus was gone but good "arousal" and good evoked potentials were still present.

Between the second and third stages the desynchronizing response to stimulation gradually disappeared in one head region after another remaining longest in temporal areas.

The third stage supervened with the development of myoclonic seizures which could be triggered by stimulation, spontaneous twitching and failing vision. The EEG revealed loss of almost all fast components, marked slowing, disappearance of bilateral synchrony, loss of the arousal response and of evoked potentials unless the stimulus was facilitated by combining it with flicker. Stimulation elicited a focal seizure discharge and clinical myoclonus which outlasted the stimulus duration. Photic driving was absent except for a peculiar "locking in" at a 3 to 4·5 per second frequency.

The last stage was characterized clinically by complete blindness and unresponsiveness. The EEG was flat with no seizure discharge or focus, with no evoked potential, no arousal or photic response. However, sensory input still triggered myoclonic seizures which then had no reflection in cortical tracings.

The reason for presenting a single case study such as this was the belief that the striking distinctness of these successive stages of electrical organization illustrated a general biological principle. We do not wish to imply that the disease did not involve a steadily continuous process of degeneration, but rather that in the course of this degeneration there were also stages of reorganization and reconstitution of central nervous function at successively lower levels of integration. To illustrate one such reorganization we may cite only one of the examples which might be drawn from these data.

It seems a fair assumption from the work of Morison and Dempsey (1942), Moruzzi and Magoun (1949), Lindsley, Schreiner, Knowles, and Magoun (1950), and Jasper (1949) that bilateral synchrony in the EEG is mediated by central pacemaker mechanisms in diencephalon and brain-stem. These diffusely inter-connected systems have also been shown to be responsible for the desynchronizing or arousal response to afferent stimulation.

It is not unlikely that in Stage II of our patient's course the electrical organization of nervous activity was directed by these central systems. Cortical activity was synchronized, local independent cortical discharges prevented (note loss of spike focus), but the cortex was adequately supplied with information over both non-specific (arousal response) and specific (evoked potentials) sensory systems. Integration was achieved on the basis of some degree of cortical-subcortical interaction. When the diffuse central systems finally failed the loss of both the excitability

modulation and interhemispheric co-ordination provided by these systems resulted in a total reorganization of the pattern of nervous integration on both electrical and behavioural levels. The cortex was no longer supplied with proper afferent information and the resulting cortico-subcortical dissociation was manifested by inco-ordinated spasms of myoclonus epilepsy at the periphery which were unreflected in cortical changes and by the presence of independent electrographic seizure discharges at the cortical level.

Summary

A case of Tay-Sachs disease was followed over an eighteen month period with clinical and electrographic observations. Four distinct stages of central reorganization or integration were described and correlation made between the clinical and electrographic manifestations at each of these stages. The presumed basis of these changes was discussed.

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CONSTRUCTIONAL APRAXIA ASSOCIATED WITH UNILATERAL CEREBRAL LESIONS—LEFT AND RIGHT SIDED CASES COMPARED

BY

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I.—INTRODUCTION

DEFECTIVE execution of constructional tasks under visual control is generally recognized as a disability which may result from a posterior cerebral lesion. On two points, however, there is no general agreement. There is disagreement as to whether the syndrome is more particularly associated with one cerebral hemisphere than the other and there is no generally accepted theory of the nature of the disability.

Following the earlier descriptions (Poppelreuter, 1917; Poetzl, 1928; Kleist, 1934; Head, 1926), this disability rapidly came to be considered as the product of a left hemisphere lesion. This resulted partly from the anatomical evidence associated with earlier cases, partly from the occasional association with Gerstmann's syndrome, and partly no doubt as a result of a ready presumption that any agnosic or apraxic disability must be associated with damage to the "dominant" hemisphere.

Certain authors (Lange, 1936; Dide, 1938; Scheller and Seidemann, 1931) pointed out that the disability may be associated with right hemisphere lesions and even claimed that the right hemisphere had an exclusive role in this respect. Similarly, Poetzl, who was one of the first to describe the disability as a left hemisphere syndrome, nevertheless took the view that the right hemisphere was specially involved in the maintenance of a temporo-spatial framework in terms of which information from the environment is interpreted.

These views attributing a special role to the right hemisphere did not, however, gain general acceptance and the notion that, except in anomalous cases, the right hemisphere is "subordinate" to the left hemisphere in respect of all forms of gnosis and praxis is still fairly general.

From the outset there has been much speculation concerning the nature of the constructional disability and this is reflected in the terminology employed by different authors. The terms visual-spatial agnosia (Scheller

and Seidemann, 1931), visual-spatial syndrome (Krapf and Courtis, 1937), temporo-spatial disorientation (Dide, 1938), clearly assume an agnosic defect. Perhaps the most common view was that there is a disturbance of the organization of motor activity *in relation* to the perception of spatial properties of the environment. This is illustrated by the terms "apractognosia for spatial articulation" (Lange, 1936) and "planotopokinesia" (Marie, Bouttier and Bailey, 1922). Kleist, to whom with Strauss (1924) we owe the most commonly used term, "constructional apraxia," took a similar view. For him, constructional apraxia was a disturbance of "a cerebral mechanism concerned with visuo-kinesthetic associations."

More recently there have been a number of communications emphasizing the frequency with which the syndrome occurs as a result of a right hemisphere lesion and suggesting that differences exist between the constructional apraxia produced by left and right hemisphere lesions. Paterson and Zangwill (1944, 1945) described 3 cases of visual-spatial agnosia associated with lesions of the right cerebral hemisphere and drew attention to the similar patterns of disability reported in earlier cases with left hemisphere lesions. McFie, Piercy and Zangwill (1950) presented 8 cases with visual-spatial and constructional disabilities in whom the lesion was exclusively (6 cases) or predominantly (2 cases) right-sided. These authors felt unable to claim an exclusive role for the right hemisphere and maintained that any such conclusion should be based, not on a few selected cases but on "the outcome of controlled clinical and experimental observation." They did, however, tentatively suggest that the pattern of visual-spatial and constructional disability in their right-sided cases differed in subtle respects from that found in left-sided cases.

Almost simultaneously Hécaen, Ajuriaguerra and Massonnet (1951) independently reported the same syndrome in cases with right hemisphere lesions but emphasized that vestibular disturbances were present in their cases and pointed to the possible role of these disturbances in the production of the visual-spatial and constructional disability. They also suggested that certain features of their patients' performance set them apart from the comparable left hemisphere syndrome: neglect of the left side of a model in copying; diagonal orientation of drawings; inability to represent perspective in drawings of three-dimensional objects; inability to articulate different parts of a two-dimensional drawing.

Critchley (1953) extensively discussed the problem of constructional apraxia on the basis of a large number of cases and came to the conclusion that the syndrome was most flagrant in bilateral cases and that the disability was possibly less severe in left hemisphere cases than in right hemisphere cases.

Duensing (1953) made a radical distinction between visual-spatial agnosia, which he associated with the right hemisphere, and the corresponding left hemisphere disability, which he regarded as a defect of

execution. For him the distinction between the two syndromes was analogous to that between receptive and expressive aphasia. The drawings of left hemisphere cases were said to be marked by more hesitations, greater simplification of outline, and to be facilitated by the presentation of a model for copying. The drawings of patients with visual-spatial agnosia on the other hand were less hesitant, were characterized by "piecemeal" representation (as described by Paterson and Zangwill) and were not facilitated by the presentation of a model for copying. It must be noted, however, that Duensing's formulation was based on differences observed between a group of 4 cases with predominantly, but not exclusively, left parietal lesions and a group of 2 cases showing visual-spatial agnosia, one of these having a right parieto-occipital lesion and the other bilateral occipital lesions. It is thus somewhat dubious whether the difference between his two groups may justifiably be attributed to the laterality of the lesions.

Denny-Brown, Meyer and Horenstein (1952) have put forward a quite different interpretation. According to these authors truly agnosic defects occur only with major hemisphere lesions but non-agnosic unilateral defects of perception may occur in association with a lesion of the parietal lobe of either side. They maintain that one of the functions of the parietal lobes is the integration of the spatial attributes of sensory impulses from the contralateral side of the body (and in the case of vision impulses corresponding to the contralateral visual field). A unilateral parietal lesion it is claimed may thus result in a unilateral defect of "spatial summation" (the term "amorphosynthesis" is also used). They suggest that unilateral neglect of space, which has frequently been reported with right hemisphere lesions, is equally common with left parietal lesions but tends to be obscured by the presence of dysphasia and agnosic defects. Their findings, based on a single case, make it "inconceivable to us that the right parietal region has some special unique significance in regard to visual space-perception."

Ettlinger, Warrington and Zangwill (1957) reported 10 carefully studied cases with right-sided posterior cerebral lesions exhibiting disturbances of spatial perception and constructional performance and concluded that the disabilities which they observed could not wholly be accounted for either by impairment of differential visual sensitivity (Bay, 1950), unilateral imperception (Denny-Brown *et al.*, 1952) or central vestibular derangement (Hécaen *et al.*, 1951; Hoff, 1953) or a combination of these. They suggest retaining the term visual spatial agnosia for this syndrome and put forward a tentative explanation in terms of restriction of the field of visual attention and disorganization of spatial orientation at a conceptual level.

The greatest single difficulty in evaluating published evidence on this problem arises from the fact that the basis upon which cases are selected varies from one report to another. In particular, there has been no study

reporting a series of relevant cases with unilateral lesions, with a basis of case selection that is strictly comparable for both right and left hemisphere lesions. The present paper communicates a series of cases exhibiting constructional apraxia in association with unilateral cerebral lesions, and the effort has been made to ensure that identical criteria should be used for the selection of right and left sided cases. The details which it is possible to present in respect of any individual patient are by no means as full here as in some previous reports. Nevertheless, it is hoped that an investigation which is carefully controlled as to the selection of cases will make some contribution to an understanding of the comparative importance of the left and right cerebral hemispheres for visual-spatial and constructional performance.

II.—Results

Incidence of Constructional Apraxia

Punch card records had been kept of all patients seen in the neurosurgical service of l'Hôpital Ste. Anne between 1947 and 1955. All these patients had been examined by one of the authors and all the cards had been punched by the examiner. The cards recorded the principal neurological findings in over 3,000 cases. All cards punched for constructional apraxia were selected and reference was then made to the detailed case notes for further information.

A total of 80 cards had been punched for constructional apraxia but, of these, 13 had bilateral lesions. We were left therefore with 67 patients with unilateral lesions exhibiting constructional apraxia. 42 of these had right-sided lesions and 25 had left-sided lesions. In order to compare the incidence of constructional apraxia in left and right sided cases it was necessary to know the total number of cases with unilateral left and right sided cerebral lesions covered by the punch card system. Accordingly, all cards punched for unilateral lesion involving the cerebral cortex or subcortical white matter were selected and these were divided into two groups according to the side of the lesion. Each of these groups was then divided into two further groups according to whether or not constructional apraxia was exhibited. The result is shown in Table I, where the contingency of

Table I.—Relationship Between Side of Unilateral Lesion and Incidence of Constructional Apraxia

		Constructional Apraxia		
		Present	*Absent*	*Total*
Side of Lesion	Left ..	25	190	215
	Right ..	42	146	188
	Total	67	336	403

$\chi^2 = 7{\cdot}55$; $p < 0{\cdot}01$

Constructional apraxia occurs significantly more frequently with right hemisphere lesions than with left hemisphere lesions.

incidence of constructional apraxia upon the side of the responsible lesion is found to be statistically significant ($x^2=7{\cdot}55$; $p<{\cdot}01$). The 42 right-sided cases with constructional apraxia constitute 22·3 per cent of all strictly unilateral right-sided cases recorded in the service, whereas the 25 left-sided cases constitute only 11·6 per cent of all unilateral left-sided cases recorded. Constructional apraxia was thus observed twice as frequently in cases with right hemisphere lesions as in cases with left hemisphere lesions.

A more detailed analysis of the data is shown in Table II. Here only unilateral post-Rolandic lesions have been considered. 37·8 per cent of all such right hemisphere lesions resulted in a constructional apraxia, as against 16·7 per cent of all such left hemisphere lesions. Analysis in terms of the distribution of lesions within each hemisphere suggests that lesions

TABLE II.—RELATIONSHIP BETWEEN INCIDENCE OF CONSTRUCTIONAL APRAXIA AND LOCUS OF LESION (BASED ON ALL CASES WITH UNILATERAL POST-ROLANDIC LESIONS)

	Side of Lesion			
	Left		*Right*	
	Constructional apraxia		*Constructional apraxia*	
	Present	*Absent*	*Present*	*Absent*
Temporal	5	40	1	19
Temp-occip. ..	1	6	0	2
Occipital	2	20	1	10
Par-temp.	6	12	3	9
Parietal	4	34	11	20
Par-occip.	5	11	18	9
Temp-par-occip. ..	2	2	8	0
	25	125	42	69
	150		111	

giving rise to constructional apraxia are considerably more restricted in their site in the case of the right hemisphere than in the case of the left hemisphere. The right temporo-parieto-occipital region and, to a lesser extent, the right parieto-occipital and parietal regions appear especially vulnerable. In contrast to this, lesions of the temporal, temporo-occipital, occipital and parieto-temporal regions more frequently result in constructional apraxia when the lesion is left sided than when it is right sided. In other words, given the side of the lesion in a case of constructional apraxia, the site of the lesion within the hemisphere could more confidently be predicted in a right hemisphere case than in a left hemisphere case. The functions impaired in constructional apraxia thus appear to be more focally organized in the right hemisphere than in the left. Considered in conjunction with the overall higher incidence of the disability with right-sided lesions, this anatomical evidence lends significant support

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to the hypothesis of right hemisphere dominance for the functions in question.

The results so far described are based on all unilateral cases exhibiting constructional apraxia, irrespective of other symptoms present and irrespective of the handedness of the patient. It was felt, however, that, in comparing the quality of the performance of the two groups of patients, it was important to exclude those in whom there was a general disturbance of consciousness to which the failure in constructional tasks might conceivably be regarded as secondary. Those patients in whom there had been evidence of general confusion were therefore excluded for the purpose of qualitative comparisons. It was also decided to exclude all left-handed patients since, in their case, it can be argued that the effects of cerebral lesions are atypical. The analysis which follows is therefore based on all right-handed cases with constructional apraxia who were free from general confusion and in whom the cerebral lesion was strictly unilateral. 42 cases conformed to these criteria: 24 with right-sided lesions; 18 with left-sided lesions.

Other Disabilities

Details of the lesions present in the 42 cases whose constructional performances are described are shown in Table III. This table also shows the incidence of hemianopia, paresis of the contralateral upper limb, dysphasia, apraxia (other than constructional), Gerstmann's syndrome, and topographical disorientation.

The relevance of dysphasia and paresis of the upper limb are discussed in detail below but brief comment on the other disabilities shown in the Table is also called for. 6 left-sided cases exhibited a general apraxia and in these cases the constructional defect could be regarded as secondary to the more general executive disability. If these 6 were excluded from consideration, the difference in the incidence of constructional apraxia in left and right sided cases would be even more striking. 7 right-sided cases showed an apraxia for dressing. The incidence of hemianopia is roughly equal in both groups of patients (about 50 per cent) and may therefore be regarded as not contributing to the difference between the two groups in the severity and incidence of constructional apraxia. Finger-agnosia was present in 4 left-sided cases and some degree of left/right disorientation in 1 more. Definite disturbance of topographical orientation was observed in 1 left-sided and 2 right-sided cases. The left-sided case tended to get lost in his own house but apparently had no special difficulty with route-finding in streets. Both right-sided cases had general route-finding difficulties. 3 further cases (1 left-sided, 2 right-sided) had difficulty in understanding a map of their own country.

Unfortunately the patients under consideration were not tested for general intellectual impairment but, as mentioned above, patients showing confusion or other disturbances of consciousness were excluded.

TABLE III

A. LEFT-SIDED CASES

Case	*Lesion Left hemisphere*	*Paresis of upper limb*	*Hemianopia*	*Gerstmann's syndrome*	*Dysphasia*	*General apraxia*	*Topographical disorientation*
1	Par.-occ. meningioblastoma	0	0	0	+	+	0
2	Vascular accident ..	0	+	0	0	0	0
3	Vascular accident ..	0	0	0	0	0	0
4	Temp. neoplasm (angiogram)	+	0	0	+	0	0
5	Temp. glioma . ..	0	0	0	0	+	0
6	Parietal trauma ..	+	+	+ Fing. agn.	0	0	0
7	Par.-temp. angioma ..	0	+	+ Fing. agn.	0	0	± With maps
8	Parietal glioblastoma	+	0	0	+	+	0
9	Front.-temp. glioma	0	+	0	+	0	0
10	Par.-temp. vasc. accident	0	0	+ L.R. dis.	+	0	0
11	Par.-occ. vasc. accident	0	+	0	+	0	0
12	Par. - temp. (EEG, motor and sensory evidence)	+	0	+ Fing. agn.	± (Parox.)	0	0
13	Temp.-par.-occ. porencephaly	0	+	0	0	0	0
14	Parietal arachnoiditis	0	0	+ Fing. agn.	0	0	+ In house
15	Temp. glioma.. ..	+	+	0	+	+	0
16	Middle cerebr. thrombosis	0	0	0	+	+	0
17	Temp. glioma.. ..	0	0	0	+	0	0
18	Temp.-par.-occip. glioma	0	0	0	+	+	0

Severity of Constructional Apraxia

32 patients (15 with right-sided lesions and 17 with left-sided lesions) were tested for their ability to draw simple geometrical figures such as a square, a diamond, a cross, a circle or a triangle. 9 of the 15 patients with right-sided lesions produced failures on this simple test but only 3 of the 17 patients with left-sided lesions.

It is of considerable interest that in the case of patients with left-sided lesions all 3 patients who showed incapacity in the simplest drawing tests also showed clinically obvious apraxia not limited to constructional

TABLE III

B. RIGHT-SIDED CASES

Case	Lesion Right Hemisphere	Paresis of upper limb	Hemi-anopia	Apraxia for dressing	Topo-graphical dis-orientation
19	Temp.-parieto-occipital glioma	+	+	0	± With maps
20	Vasc. accident	0	+	0	0
21	Temp.-par.-occip. necrosis	0	+	+	0
22	Par.-occ. astrocytoma	+	+	+	0
23	Temp.-par.-occip. astrocytoma	+	+	0	+
24	Metastases (R. hemisphere only)	+	± Inf. quad.	0	0
25	Int. carotid thrombosis	+	± Partial	0	0
26	Occip.-temp. gliosis	0	± Inf. quad.	+	+
27	Occip. lobectomy	0	+	0	0
28	Occip. trauma	0	+	0	0
29	Int. carotid thrombosis	0	0	0	0
30	Temp.-par. glioma	+	0	0	0
31	Parietal trauma	0	0	0	0
32	Par.-occip. astrocytoma	+	0	0	± with maps
33	Occip.-par. glioma	0	+	0	0
34	Par.-temp. glioma	+	0	+	0
35	Post-Rolandic (EEG and motor evidence)	0	0	0	0
36	Parietal glioma	+	+	0	0
37	Temp.-par.-occip. meningioma	+	0	+	0
38	Parietal glioma	+	0	0	0
39	Par.-occip. glioblastoma	+	+	+	0
40	Par.-temp. glioblastoma	+	+	0	0
41	Post. cerebr. thrombosis	+	+	0	0
42	Par.-occip. glioma	0	+	+	0

performances. There is thus not one patient in the left-sided group whose failure on very simple drawing tests could not be attributed to a more general apraxia; whereas in the right-sided group there are 9 out of 15 patients (or 6 out of 12, if patients with apraxia for dressing are excluded) showing these gross constructional failures without any general apraxia.

It is evident therefore that the impairment of drawing tends to be more severe in the right hemisphere cases than in the left hemisphere cases.

5 left-sided cases and 10 right-sided cases were tested for their ability to copy matchstick models. These models varied in complexity from simple geometrical figures such as a triangle or a square to two-dimensional representations of a house and a cube (made with 11 and 9 matchsticks respectively). The results are shown in Table IV. A total of 14 out of 15

TABLE IV.—MATCHSTICK COPYING TEST

Left Hemisphere Cases

	House	*Cube*	*Simple forms*	*Total*
Tested.. ..	3	4	2	9
Correct ..	2	1	1	4
Failure ..	1	3	1	5

Right Hemisphere Cases

	House	*Cube*	*Simple forms*	*Total*
Tested.. ..	7	4	4	15
Correct ..	1	0	0	1
Failure ..	6	4	4	14

failures were made by the right hemisphere cases, as against 5 out of 9 by the left hemisphere cases. Here, as in the drawings, the right hemisphere cases are distinctly more impaired than the other group.

Comparative Performance in Copying and Spontaneous Drawing

Figs. 1 and 2 show spontaneous drawings of a house and copies of a drawing of a house for all patients who were tested for both performances. In 7 of the relevant 10 cases with left-sided lesions, the copy was unequivocally superior in construction to the free drawing (Cases 3, 6, 7, 10, 11, 15 and 16). In the remaining 3 cases the two performances were of approximately equal quality. 7 right-sided cases were tested both for free drawing and for copying a drawing of a house and, of these, only 2 produced copies which might fairly be judged superior to the corresponding free drawings (Cases 19 and 28).

If figs. 1 and 2 are compared, it is evident that the two groups of patients can be distinguished far more readily by their copies than by their free drawings. The copies executed by left-sided cases are far more recognizable as drawings of a house than are the corresponding drawings of right-sided cases. The same cannot be said of the spontaneous drawings of a house executed by the two groups. The left hemisphere group are perhaps somewhat superior in this task but the difference is by no means as strikingly obvious as that to be observed between the copies.

It appears therefore that the provision of a model to copy considerably facilitates the drawing ability of patients with left hemisphere lesions but has little effect in right hemisphere cases. This is in conformity with Duensing's suggestion.

Fig. 3 shows attempts at copying a drawing of a house made by those right hemisphere cases who did not attempt a corresponding free drawing. Attempts at copying a drawing of a cube are shown for both groups in fig. 4. These results are referred to below.

Complexity of Structure

Although in many cases the drawings produced by right and left sided

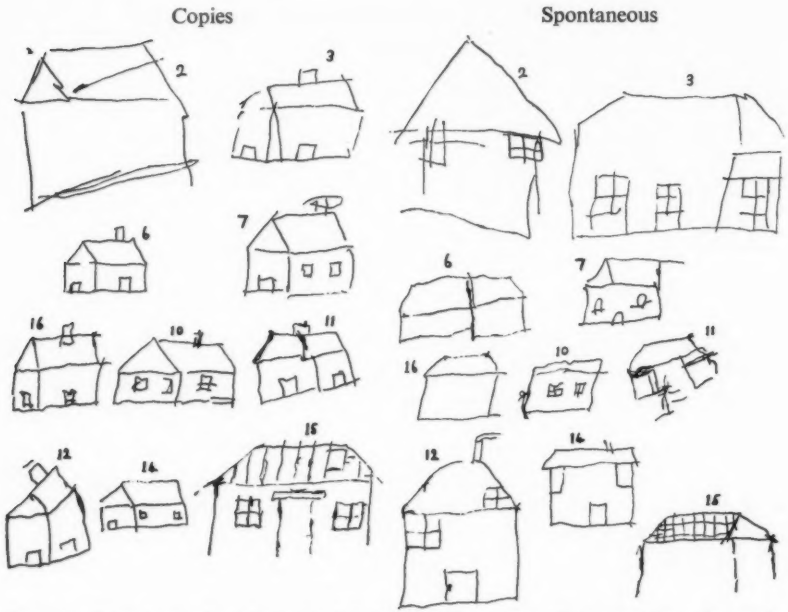

FIG. 1.—Drawings of a house by left hemisphere cases. The numbers refer to the cases listed in Table III.

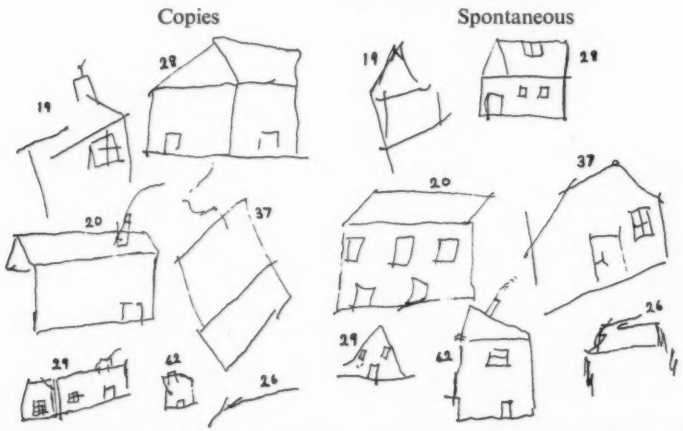

FIG. 2.—Drawings of a house by right hemisphere cases. The numbers refer to the cases listed in Table III.

cases are not individually distinguishable, there appears to be one type of drawing which is typical of the right hemisphere syndrome. This is the

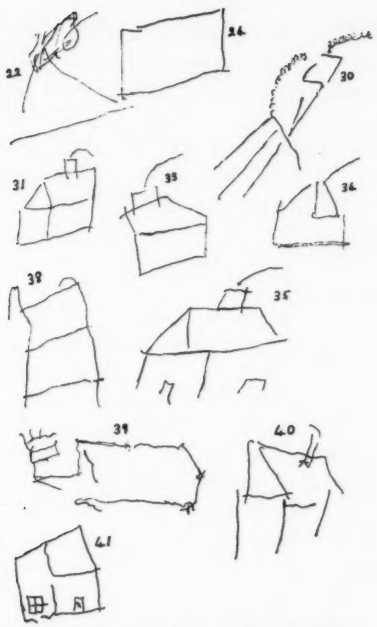

FIG. 3.—Further copies of a house by right hemisphere cases. The numbers refer to the cases listed in Table III.

attempt at a copy which, although unrecognizable as a picture, is comparatively complicated in structure. This can be seen in the copies of a house by Cases 30 and 39 and the copies of a cube by Cases 25, 30 and 37. Left-sided cases producing unrecognizable copies tended to produce more simply structured drawings.

This tendency for the unrecognizable copies produced by the two groups to differ in complexity can be quantified. 6 of the attempts by left-sided cases to copy a drawing of a cube and 10 of those by right-sided cases could fairly be judged as unrecognizable (in fig. 4: Cases 1, 3, 5, 9, 11, 15, 19, 22, 23, 25, 26, 30, 37, 38, 39, 42). The copies of a cube have been selected for this analysis in preference to copies of a house since all but one of the left hemisphere copies of a house were fully recognizable. A count was made of the number of lines constituting each copy of a cube made by our patients. In making this count, overscorings of the same line were not counted but continuously drawn lines which abruptly changed direction were counted as two lines. Continuous curves were counted as single lines, as were interrupted straight lines. The mean number of lines for the left hemisphere group of unrecognizable drawings was 4·83 and for the corresponding right hemisphere group 8·9. A "t" test showed this difference to be statistically significant ($p < \cdot 05$).

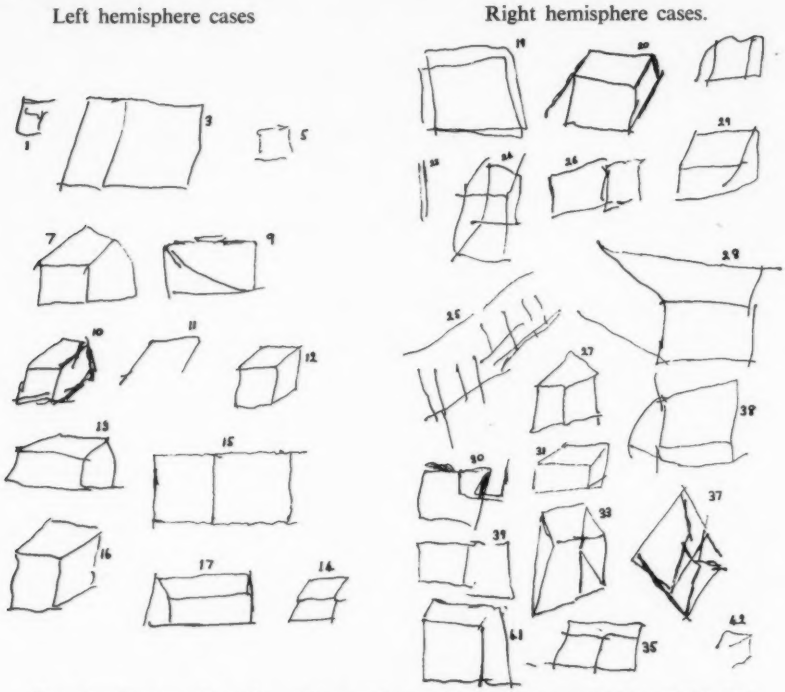

FIG. 4.—Copies of a cube. The numbers refer to the cases listed in Table III.

Among the *recognizable* copies of a cube there was no significant difference between the mean number of lines used by the right and left sided groups (9·44 and 8·86 respectively). It is instructive to note that, within the group of right hemisphere cases, the mean number of lines used in unrecognizable drawings (8·9) is not significantly different from the number used in recognizable drawings (9·44). But within the left hemisphere group the mean number of lines used in unrecognizable drawings (4·83) is about half the number used in recognizable drawings (8·86). This suggests that severe incapacity in left-sided cases tends to result in a more simplified drawing, whereas in right-sided cases severe incapacity tends to result in a drawing which, although disorganized, is comparable in complexity to the drawing which serves as a model.

Orientation of Drawings

A further difference between the two groups which may be tentatively suggested concerns the orientation of the drawings on the paper. In copying drawings of a cube and of a house, certain right hemisphere cases orientated their drawings diagonally on the paper. This is obvious in

some of the productions of Cases 25, 30 and 37, and questionably apparent in Cases 19 and 42. In Case 37 the tendency is apparent in all three of the available drawings. The only left-sided case in whom this tendency is even questionably apparent is Case 11.

It is of some interest that, although this tendency can be seen in drawings both of a house and of a cube, it is not obtrusive in drawings of a bicycle (not shown here). The tendency is perhaps encouraged by the diagonal lines which are conventionally necessary to represent a 3-dimensional object on a 2-dimensional surface: that is to say that the orientation of particular lines may determine the orientation of the drawing as a whole. This finding is related to Hécaen, Ajuriaguerra and Massonnet's suggestion that right hemisphere cases find special difficulty in representing perspective.

Broadly similar spatial confusion may be seen in the intimate structure of the drawings of both groups of cases. The simplest example is perhaps in the copy of a house by Case 12 and the spontaneous drawing of a house by Case 42. In both of these drawings the chimney has been drawn at right angles to the diagonal line representing the top of the roof. An inappropriate "frame of reference" has evidently been used for the perpendicular orientation of the chimney. It would appear, however, that confusion of this type affecting the orientation of the *drawing as a whole* occurs more frequently in right hemisphere cases than in left hemisphere cases.

"Closing In" Effect

Ideomotor or ideational apraxia occurred in 6 of our 18 constructional apraxia cases with left-sided lesions. All of these 6 showed in their constructional performances a marked tendency either to superimpose the constructed copy upon the model or to overlap the model with the copy ("closing-in" effect of Mayer-Gross, 1935). These were the only left-sided cases to show the "closing-in" effect. 2 of the 24 right-sided cases also showed the "closing-in" effect and both of these exhibited apraxia for dressing. 5 other right-sided cases exhibited apraxia for dressing without a "closing-in" effect. It can thus be said that all of our patients with a "closing-in" effect in their constructional performances also exhibited some other kind of apraxia and that, in the case of left-sided lesions, "closing-in" was always accompanied by frank apraxia for other than constructional performances. We do not wish to claim special significance for this finding but feel that it should be put on record.

Unilateral Neglect

Neglect of the left side was an identifiable factor in the impaired constructional performances of 7 of the right-sided cases. In the left-sided cases neglect of the right side could be identified in the drawings of 2 cases. This observation is based on all available drawings executed by our two

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groups of patients, including drawings of bicycles, drawings of a man and simple geometrical forms, as well as the drawings shown in figs. 1 to 4. Unilateral neglect was also apparent in the behaviour (reading, counting, ignoring the left side of the body) of 7 right-sided cases who did not show this deficit in their constructional performances. Comparable behavioural evidence was not observed in any left sided cases. 14 of the 24 right sided cases therefore exhibited some kind of neglect for the left side of space, as against 2 of the 18 left-sided cases who exhibited some kind of neglect for the right side of space.

III.—Discussion

It is clear from these results that the term "constructional apraxia" may be applied descriptively to disabilities occurring in association with unilateral lesions of either cerebral hemisphere. Our results suggest that this type of disability occurs twice as frequently with right-sided as with left-sided lesions and that the defect is more severe in the former group. This is in accordance with Critchley's suggestion (1953) that constructional apraxia is more readily demonstrated in cases of disease of the subordinate hemisphere.

We must now consider possible explanations of the higher incidence and greater severity of constructional apraxia in right-sided cases.

One possibility is that in left hemisphere cases constructional apraxia may be masked by other defects such as aphasia and paresis of the dominant hand. This must be considered carefully since the present study was carried out *post hoc* and was restricted to patients already diagnosed as exhibiting constructional apraxia. 10 of our 18 left-sided cases were dysphasic and the dysphasia included a comprehension defect in all 10 cases. It is thus clear that dysphasia does not preclude the identification of a constructional apraxia. However, the possibility remains that, in some cases, constructional apraxia was masked by an unusually severe dysphasia and so did not appear in our records. Nevertheless, although it is conceivable that the incidence of constructional apraxia might be artificially lowered in left-sided cases, it would be difficult to account in this way for the reduced severity of constructional apraxia in this group. On the contrary, if dysphasia tends to mask the constructional disability, the milder cases in particular would tend to be obscured, thus artificially increasing the average severity of constructional apraxia in left-sided cases.

A similar argument applies to the possibility that constructional apraxia was masked by paresis of the preferred hand in some cases of left hemisphere lesion. Although the incidence could be reduced if the disability of milder cases were mistakenly attributed to the paresis, this should not reduce the apparent severity of the defect. Indeed the selective factor might be expected to increase the apparent severity of the constructional disability. Moreover, all cases that had incapacitating paresis of the preferred hand were also tested with the non-preferred hand.

A further possible selective factor is the failure to test for constructional apraxia in patients with paresis of the preferred hand or with aphasia. Since all patients entered on the punch cards were examined by one of the authors, it can be said with some confidence that this is an unlikely explanation. However, in order to exclude this possibility as objectively as possible, the following control procedure was carried out. All cards punched for both aphasia and hemiplegia but not punched for constructional apraxia were selected. There were 20 such cards. Reference was then made to the detailed case notes of these 20 patients. It was found that 12 of these had been carefully examined for constructional apraxia with negative results. All 8 that had not been so examined had gross clouding of consciousness and the aphasia had been either severe and obvious or else (more frequently) inferred from the history given by relatives. Against this indirect evidence suggesting that the differences between our left and right-sided cases are not adequately accounted for by artifacts of case selection, must be set the observation that the incidence of paresis of the upper limb is higher in our right hemisphere cases (14 out of 24) than in our left hemisphere cases (5 out of 18). Accordingly, our conclusions as to the relative incidence of constructional apraxia with left and right sided lesions are provisional only. The difference in the severity of the disability is, however, less equivocal.

Denny-Brown, Meyer and Horenstein (1952) have suggested that disabilities of the type reported here may be attributed to "amorphosynthesis." We do not propose to discuss these authors' distinction between amorphosynthesis and agnosic defects but we must point out that their interpretation can be applied to our results only if it is assumed that the differences between our two groups are attributable either to selective factors or to the presence of agnosia plus amorphosynthesis in left-sided cases but amorphosynthesis only in right-sided cases. The first of these alternatives has already been discussed and the second is improbable in view of the greater severity of the disability in right-sided cases.

Two further possibilities remain to be considered. Constructional apraxia may result from impairment of a function which is bilaterally although unequally represented. Alternatively, constructional apraxia may be a disturbance which is functionally different according to the hemisphere involved.

It is clear that some of our findings are quite consistent with the first of these two alternatives. Constructional apraxia occurs more frequently and with greater severity in right-sided cases and we also have evidence suggesting that functions impaired in constructional apraxia are more focally organized within the right hemisphere than within the left. This is what would be expected if the right hemisphere were dominant for the functions in question.

Nevertheless, despite this evidence, such an interpretation presents

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difficulties. Other focal "intellectual" signs of cerebral dysfunction are generally regarded as having strictly unilateral significance, except in rare and anomalous cases. Thus aphasia, ideomotor apraxia, finger agnosia, object agnosia, acalculia and left-right disorientation are rarely attributed to a right hemisphere lesion, and it is by virtue of this fact that the right hemisphere in right-handed people has come to be designated the minor or subordinate hemisphere. It has been argued that language may be represented bilaterally in left-handed people (Chesher, 1936; Subirana, 1952; Hécaen and Piercy, 1956) but this is by no means generally accepted (Ettlinger Jackson and Zangwill, 1955, 1956) and also those who claim bilateral representation of language in left-handed people also suggest that dysphasia in these cases is mild and transient. Bilateral focal but unequal representation of a special group of perceptuomotor skills would therefore be a little surprising, although not theoretically unacceptable.

The hypothesis that constructional apraxia may result from a disturbance of one of two different functions, and that these two functions are represented respectively in the right and left hemisphere demands for its support evidence of differences between the two syndromes other than differences in severity and frequency. The differences which we have been able to show are comparatively subtle. They have been educed from the groups as a whole and, although certain types of performance appear more typical of right hemisphere dysfunction than left, it would not usually be possible to infer the side of the responsible lesion from constructional performance alone. Two of the differences described above could not readily be equated with differences in severity. Thus the observation that the presentation of a model to copy facilitates the drawings of left hemisphere cases but not those of right hemisphere cases suggests that different or additional functions are impaired in the right hemisphere group. Similarly, an increase in the severity of the constructional disability has different consequences in the two groups. In the left hemisphere group the more impaired patients tend in their copies of drawings towards gross simplification of outline, whereas in the right hemisphere group the more impaired patients tend towards erroneous elaboration of detail. This observation is frankly inconsistent with the hypothesis of a difference in severity alone.

Both of these findings are consistent with the hypothesis that, in general, constructional apraxia associated with right hemisphere lesions involves greater impairment of perceptual functions than is the case in the left hemisphere syndrome. A corollary hypothesis is that, when left hemisphere cases show severe constructional apraxia, this results from comparatively greater impairment of executive functions than is usual in right hemisphere cases. Among our patients, the only 3 left-sided cases to fail on the very simplest drawing tests also had a clinically obvious apraxia which extended beyond constructional performances, and in these

cases it may be that the constructional defect was secondary to the general apraxia. It seems right to enquire therefore whether constructional disability resulting from a left hemisphere lesion may not frequently be a minor or special form of general apraxia. Unfortunately we lack information as to how frequently ideomotor apraxia as described by Liepmann is unaccompanied by constructional disability in cases of unilateral left hemisphere lesions. If this were never or hardly ever the case, then the hypothesis would receive further support. We may add that, if this evidence were forthcoming, it would be a reasonable presumption that, at least in some cases, a lesion might just fail to produce an ideomotor apraxia but might nevertheless be sufficient to produce impairment at a higher level of intellectual organisation, i.e. on constructional tasks. Analogous "subclinical" disability may frequently be observed in the sphere of language. A progressive cerebral lesion may at first produce definite impairment in language-intelligence tests and only at a later stage result in a dysphasia as ordinarily understood (McFie and Piercy, 1952).

These considerations, however, await further enquiry and it is important not to over-simplify the problem. Thus it would be naïve to suppose that perceptual processes are in no respect impaired in the constructional apraxia of left hemisphere origin since, for example, it may reasonably be argued that ideomotor apraxia in some sense involves faulty perception. Nor can one afford to ignore the fairly frequent association of left hemisphere constructional apraxia with left-right disorientation, finger-agnosia or disturbance of topographical orientation. We believe cognitive impairment contributing to constructional apraxia to be greater in the right hemisphere syndrome, but we would not attribute an exclusive role to the right hemisphere in this regard. The most that we wish to claim for this study is that it is based on all appropriate cases admitted to a particular neurosurgical unit over a period of eight years, and that the results strongly suggest that the right cerebral hemisphere has a special, non-subordinate role in the cognitive functions necessary for normal constructional performance.

Summary

(1) Studies of constructional apraxia are briefly reviewed in relation to the respective roles of the two cerebral hemispheres.

(2) On the basis of records kept in a particular neurosurgical unit over a period of eight years, an analysis is presented of the incidence, severity and nature of constructional apraxia resulting from unilateral cerebral lesions.

It is observed that the disability is more frequent and more severe in right hemisphere cases and that the localization of responsible lesions tends to be more restricted in right hemisphere cases. Qualitative differences between the constructional performances of left and right hemisphere cases are analysed and discussed.

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(3) It is concluded: (*a*) that the differences between the two groups in the severity and frequency of the disability cannot be accounted for by the masking effect of paresis and dysphasia or by unilateral imperception; (*b*) that the qualitative differences observed cannot be attributed to differences in severity alone; (*c*) that the right cerebral hemisphere in right-handed people has a special non-subordinate role in the cognitive functions involved in normal constructional performance.

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VISUAL-CONSTRUCTIVE DISABILITIES ASSOCIATED WITH LESIONS OF THE LEFT CEREBRAL HEMISPHERE

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I. INTRODUCTION

IN a series of papers (Paterson and Zangwill, 1944, 1945; McFie, Piercy and Zangwill, 1950; Ettlinger, Warrington and Zangwill, 1957) we have presented an analysis of the disabilities of construction associated with lesions of the right cerebral hemisphere. In brief, the syndrome described consists of disorganization of construction, drawing, etc., in a characteristic way; failure on tasks involving spatial analysis, frequent failure on tasks requiring an even simpler maintenance of orientation, e.g. counting scattered dots; and in many cases "apraxia for dressing" and topographical memory loss. We have also noted that this syndrome is characteristically associated with lesions of the parieto-occipito-temporal region of the right (minor) hemisphere. While many of the patients have also had visual field defects, neglect of the left half of the body, or vestibular disturbances of central type (cf. "Funktionswandel" of Bay, 1954; amorphosynthesis of Denny Brown *et al.*, 1954; vestibular derangement of Hécaen *et al.*, 1951) we have argued that none of these is invariably related to the syndrome, which appears rather to demand an appreciable element of conceptual spatial loss. As this is commonly manifested in performances under visual control, we have hitherto retained the term "visual-spatial agnosia" to describe the deficit. Essentially the same syndrome has been described under the term "apractognosia" by Hécaen *et al.* (1954, 1956) following excision of the supramarginal and angular gyri and the posterior portion of the superior temporal gyrus on the right.

At the same time, we have been aware that disabilities of construction, manipulation, drawing, etc., have commonly been held to be symptoms of parietal lobe dysfunction, without distinction as to the side affected. Thus in Critchley's (1953) monumental survey of the parietal lobes, the table (p. 392) which summarizes the disabilities associated with *unilateral* (regardless of side) lesions includes "constructional apraxia (?)": the mark of interrogation is sustained by omission of the disorder from those

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associated with dominant hemisphere lesions (p. 394), while it reappears in association with minor hemisphere lesions (p. 396). In his description of constructional apraxia (Ch. VI) Critchley makes it clear that, since Kleist's first use of the term, there has been continued discussion concerning the precise nature of the disability, revolving chiefly round the question whether it was primarily an executive or a perceptual deficit. On the other hand, since Kleist's (1934) description of constructional apraxia as "a disturbance which appears in formative activities (arranging, building, drawing) and in which the spatial part of the task is missed, although there is no apraxia of single movements," most authors have accepted a *spatial* derangement as an integral feature of the disability. Mayer-Gross (1936*b*), however, has doubted whether it plays a significant part: "in most cases, the patients are able to recognize or imagine direction, localization and extension in space: they have no disturbance in perception of visual, tactile or vestibular space." This is evidently a very dissimilar condition from the syndrome of visual-spatial agnosia, and suggests that constructional apraxia may have an altogether different basis. Mayer-Gross considered the disturbance to be fundamentally in "activity space" (Wirkraum), adding that "one has however to realize that it implies a specific visual factor inseparable . . . from the motor element."

The significance of the site of the lesion responsible for the disability was not generally considered relevant to the discussion: many of the cases described (cf. Lhermitte and Trelles, 1933; Mayer-Gross, 1935, 1936*a*) were evidently suffering from a generalized dementia, and, in the few post-mortem examinations reported, lesions were generally bilateral. Nevertheless, the common association of the disability with acalculia, alexia, finger agnosia and receptive language disorders resulted in agreement that it frequently occurred with left parietal lesions.

There have been few comparisons between the disabilities resulting from comparable lesions of left and right hemispheres. Hêcaen *et al.* (1953) have reported a series of 50 cases of parietal lobe tumours, 22 of the left side and 28 of the right. They noted with surprise that while 12 of the cases with right-sided lesions showed visual-constructive disabilities (described by them as "constructional apraxia"), only 3 of the left-sided group did so. Although they found lasting disturbances of body-scheme and "apraxia for dressing" only in association with right-sided lesions, they felt they were not in a position to distinguish between the types of constructional disability arising from lesions on different sides. In a series of 17 posterior cerebral excisions, Hêcaen *et al.* (1954) found that the 2 cases of left-sided excision, though both in left handers, showed no disturbance of spatial perception. In a further analysis of the disabilities of these patients, Hêcaen *et al.* (1956) observed that "there is a strange difference, which is not easily understood, between the functions of the two parietal lobes. . . Ideational and ideomotor apraxias form part of the

clinical picture due to left-sided lesions. The apraxia for dressing is met with only in right-sided lesions. The visuo-constructive disabilities are integral parts of both the right and the left syndrome, and the exact difference between these two types of constructional apraxia is not yet clearly established." Arseni *et al.* (1958) have reported a purely statistical survey of 32 patients with parietal tumours: excluding the left handers, of 9 with left-sided lesions 6 showed "constructional apraxia," of whom 4 showed "spatial agnosia," one showed "spatial disorientation" and one loss of topographical memory, but none showed "apraxia for dressing." Of the 20 with right-sided lesions, all showed "constructional apraxia," 18 showed "spatial agnosia," 2 showed "spatial disorientation," 12 loss of topographical memory, and 15 "apraxia for dressing." The authors do not make any statements of the criteria used to establish these categories, but the differences in grouping of the signs are of interest. Reitan (1959), reviewing the results of psychological testing of some 2,000 neurological patients, states that "the frequency of constructional dyspraxia (as shown in difficulty in copying accurately common spatial configuration) is much greater in patients with damage of the right cerebral hemisphere than in patients with damage of the left cerebral hemisphere."

The present communication describes a series of patients with lesions in the left cerebral hemisphere, in whom constructional disability was a predominant psychological manifestation. All of the patients were right-handed.

II. Cases

Case 1 (N.H. 1874).—A commercial artist, aged 57, was admitted complaining of speech difficulty, numbness of the right hand, and general mental deterioration.

For about a year before admission his wife had noticed a slight falling-off in his powers of concentration and retention, reaching proportions which were quite unusual for him. Three months ago, he was for a few moments unable to speak; a month later he had the first of a number of attacks of burning pain in the right hand, following which it had remained numb and slightly clumsy. At the same time a persistent language defect became evident, and his spelling and mental arithmetic also began to deteriorate. He had also some difficulty in dressing himself correctly; and occasionally a generalized morning headache.

On neurological examination his fields of vision were full, and visual acuity 6/12 on the right and 6/9 on the left (corrected). There was slight marginal blurring of the optic discs. There was hypalgesia on the right side of the face, and some weakness on voluntary movement. There was slight increase in tone and tendon reflexes in the right limbs, and absence of abdominal reflexes on this side, but both plantars were extensor. The whole right side of the body was hypæsthetic to touch, and in the right hand and foot, vibration and position sense were diminished.

On psychological examination his premorbid intelligence was placed in the superior range (Terman-Merrill Vocabulary score: 35). He showed a mild, but clear-cut receptive dysphasia and slight difficulty in reading and writing. He was unable to sort on Weigl's test, and showed some impairment on Wechsler's Similarities test (score: 11).

Performance on *visual-constructive tasks* was considerably impaired. His score on Kohs' block designs (53) was below the level expected. His copying of geometrical

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figures was poor; and his freehand drawing was surprisingly poor, considering his profession as an artist. There was no evidence of topographical disability, and his drawing of a map of England, though over-simplified, was correct in general proportion.

There was no evidence of apraxia of a "lower" type; but he showed certain perceptual disabilities. Thus, his Matrices score was only 44 (average adult), and he found the problems very difficult, taking one hour ten minutes over the test. He had difficulty in mentally reversing the position of clock hands; counted hours anticlockwise (e.g. from 9 to 5 as five hours); and had difficulty in distinguishing his own right and left.

He was exceedingly aware of his disabilities, and was prone to "catastrophic" reaction to failures on tests.

Air encephalography demonstrated the presence of a left parietal expanding lesion, and a right temporal decompression was made. The patient died a month later.

At post-mortem examination a cystic glioma, measuring about 4 cm. in either direction, was found in the cortex of the left inferior parietal lobule (Fig. 1, Plate XXXII).

Case 2 (N.H. 12055).—A maintenance engineer, aged 56, was admitted with complaints of attacks of dizziness, with loss of consciousness, and episodes of mental confusion and speech disorder.

While at work two weeks before admission, he suddenly "came over dizzy," and found himself unable to understand speech or to express his own thoughts. Returning from his doctor's house, he felt uncertain as to his whereabouts; "everything looked strange and unfamiliar"; but he arrived home safely, and lost consciousness for about a quarter of an hour. These episodes of confusion had recurred; and with them he had noticed that in the right half of his fields of vision a rainbow of colours appeared, superimposed upon but not obscuring the objects seen. Between these episodes, he had still a slight difficulty in speaking, and occasional headaches, but otherwise no complaints.

On neurological examination he had a right upper quadrantic hemianopia, and an equivocal right plantar response, but otherwise no abnormality. V.A.R. 6/6: V.A.L. 6/9.

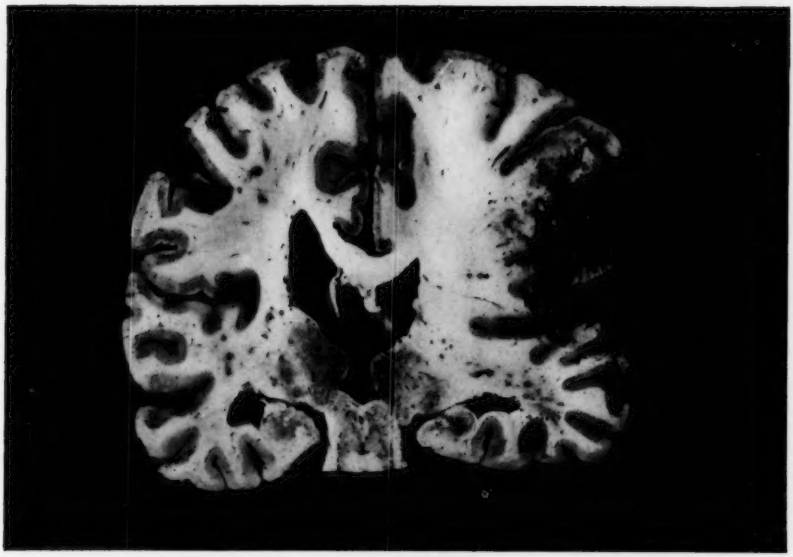
On psychological examination he showed a moderate degree of general impairment, from a previously bright normal level: his digit span was reduced to 5, he failed Weigl's sorting test, and he had some difficulty in interpreting complex pictures: arithmetical ability was not markedly impaired. His dysphasia was moderately severe: he was able to understand and carry on a normal conversation, but verbal learning, reading, and writing were very poor.

His disabilities were also marked on *visual-constructive tasks*. He was able to produce only four block designs within the prescribed time; and his freehand drawing was poor. In his drawing of the road junction at Shepherd's Bush (near his home) he made a conspicuous error in representing the Uxbridge Road, as actually running on to the Green; but the relationships of all the roads were correctly represented, as were the features in a plan of his ward, and even the indication of perspective in drawing a chair.

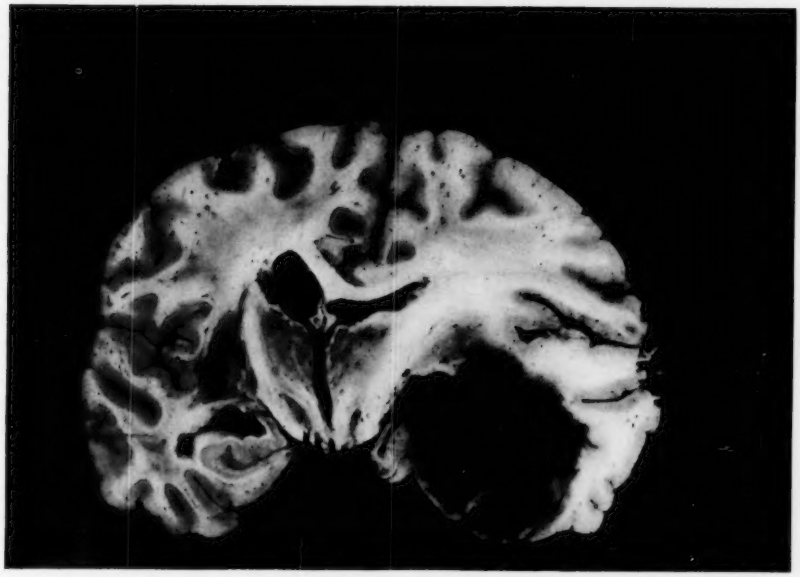
There was no evidence of dyspraxia, either in concrete actions or in pantomime, nor of dressing disability. He represented horizontal and vertical correctly, and made no errors in counting scattered objects or grouped cubes, nor in problems involving direction and points of the compass.

He was well aware of the main features of his impairment, and was able to judge whether or not his performance was correct.

Air encephalography showed a slight shift to the right of the interventricular



(a) Case 1.



(b) Case 2.

FIG. 1.—Photographs of sections of cerebral hemispheres.

To illustrate article by J. McFie and O. L. Zangwill.

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septum, and compression of the left lateral ventricle; but a biopsy revealed no abnormality, and the patient was discharged.

He was readmitted, six months after his first admission, drowsy, double incontinent, aphasic, and with a right hemiplegia; and died a month later.

At post-mortem examination a glioma was found in the left temporal lobe, extending from near the temporal pole to within 5 cm. of the occipital pole (fig. 2).

Case 3 (N.H. 37018).—A housewife, aged 47, admitted on account of attacks of vertigo, weakness of the right hand, and speech difficulty.

Three years before admission she had a severe attack of vertigo, diplopia and vomiting which lasted nearly all day. During the next year, she had a number of similar, though less severe, attacks, involved gross nystagmus to the right. Six weeks before admission, while shopping, her right hand became suddenly unable to hold the basket, and she became unable to speak. She returned home without difficulty, but had great trouble in getting the key into the lock, and in turning it. Later she had clonic spasms in the right arm, and lost consciousness for half an hour. She continued to have slight difficulty in expressing herself, and had frequent headaches.

On neurological examination she showed no reduction of visual acuity or field defect. The right corneal reflex was reduced, as was sensation over the arc of the third division of the fifth nerve. There was weakness of the right side of the face, and of the right limbs. Tendon reflexes on the right side were exaggerated, with brief ankle-clonus, and equivocal right plantar response. There was a marked degree of cortical sensory loss over the right side of the body.

On psychological examination her premorbid intelligence was placed in the bright normal range (Bellevue Vocabulary score: 30). Besides a moderate receptive dysphasia, dyslexia and dysgraphia, she showed evidence of a moderate degree of general intellectual impairment: digit span was reduced to 5; she was unable to do Weigl's sorting test; and her arithmetical ability was impaired, though she was not frankly dyscalculic.

On visual-constructive tasks her impairment was also marked. She was able to copy only the first of the block designs; she copied matchstick patterns poorly; and took more than the normal maximum time to assemble the Bellevue Manikin. Her freehand bicycle and copies of drawings were also of poor quality. On being required to indicate different sides of her body, she showed a moderate degree of right-left disorientation; but she was able to hold a stick accurately in horizontal and vertical positions. Her account of topography in the neighbourhood of her home (Brighton) was accurate, although she made some "left-right" errors in assigning compass directions (e.g. said Black Rock was west of Palace Pier), though it was evident from her descriptions that she knew in fact where these were.

On the *executive* side, she had some finger dyspraxia, but had no difficulty in demonstrating the use of objects, in fact or in pantomime. On the *perceptual* side, she showed no evidence of visual-spatial disability: she counted cubes and scattered objects correctly, and reproduced the chief spatial relationships in designs she was required to copy.

At operation a fairly well-demarcated gliomatous mass was found in the convexity of the left parietal cortex, stretching from the central sulcus about 5 cm. posteriorly, and measuring about 7 cm. from its upper to its lower borders. It was dissected out and found to merge with brain substance to a depth of about 5 cm.

Case 4 (N.H. 26057).—A retired public assistance officer, aged 62, who complained of disturbance of vision and mental deterioration.

Six months previously he had first noticed difficulty in reading and writing, and

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he began to make errors in spelling: this progressed, so that he had to read word by word. At the same time calculation deteriorated, so that he became unable to do the simplest sums. On one occasion, about a month before admission, he was unable to say what he wanted to, "he talked scribble," as he put it; but generally had little trouble with speech. Recently he had found placing knives and forks on the table difficult; but had no difficulty in finding his way about or in getting dressed.

On neurological examination he showed a macula-splitting right homonymous hemianopia, but visual acuity was 6/9 in the remaining half-fields, and there was no papillœdema. Motor and sensory systems, and reflexes, showed no abnormality.

On psychological examination his vocabulary level (Wechsler-Bellevue score: 40) indicated a superior premorbid intelligence. He showed a mild nominal dysphasia, but his flow of speech, and his comprehension, were good. He showed also a mild alexia and agraphia of receptive type, and marked dyscalculia.

He showed marked impairment on *visual-constructive tasks*, particularly in freehand drawing. He was able to do only the first four block designs, and was quite unable to cut a star-shape out of a piece of paper. At the same time, he was able adequately to represent the plan of the ground floor of his house, and to hold a stick accurately in horizontal and vertical positions. He did not show any difficulty in right-left discrimination.

He showed evidence occasionally of a mild dyspraxia, having some difficulty in knotting his tie or dressing gown cord. On the perceptual side, he was able to count scattered objects, but failed to count piles of cubes correctly *largely on account of his dyscalculia:* he also showed some difficulty in interpreting pictures.

He was aware of the main features of his disability, and was able to judge the correctness or otherwise of his solutions.

Ventriculography demonstrated a shift to the right of the left lateral ventricle, while the left temporal horn showed a filling defect in its proximal portion: appearance of a space-occupying lesion in the left temporo-parietal region, which was also seen to be slightly calcified. Biopsy showed this to be a grade III astrocytoma, and the patient died three weeks later: post-mortem examination was not made.

Case 5 (N.H. 29536).—A farm labourer, aged 47, was admitted complaining of severe frontal headaches for a month.

He admitted that his vision had deteriorated, and his wife observed that his memory had deteriorated over the past few months.

On neurological examination he showed a right homonymous hemianopia, with visual acuity 6/24 and 6/36 in the remaining left half-fields. There was bilateral papillœdema, with several small hæmorrhages on the right. There was some fine nystagmus on looking to the right, but no other defect of external ocular movements. The right corneal response was diminished, and on Weber's test the sound referred to the right ear. The right limbs showed slight spastic weakness, and reflexes on that side were brisker: there was unsustained ankle clonus on the left, sustained on the right. Pain and touch were apparently perceived equally on both sides, but there was suppression on the right to bilateral simultaneous stimulation.

On psychological examination he was inclined to be drowsy, and at times confused, but was able to respond to questions quite well. He showed no dysphasia, but was practically acalculic, alexic and agraphic. His vocabulary score (Bellevue scale: 20) placed his premorbid intelligence in the average normal range, but he failed Weigl's sorting test.

He showed also marked disabilities in the *visual-constructive* sphere. He could do only the first two block designs, and had difficulty in constructing a star out of match sticks. Freehand drawing was of very poor quality, but he was able to

represent very well the road junction near his home, and to indicate the positions and directions of the half-dozen roads concerned. He showed right-left disorientation both on himself and on the examiner, and some finger agnosia: but he was able to represent horizontal and vertical co-ordinates adequately with a stick. He also did the Stanford-Binet paper cutting item very well.

On the *executive* side, he showed no disability; on the *perceptual* side, he counted scattered objects and piles of cubes very well, but had considerable difficulty in interpreting pictures and scored only 15 on Raven's Matrices.

Biopsy in the left parieto-occipital region demonstrated the presence of a grade II oligodendroglioma. This responded to deep X-ray therapy, and the patient was well and working a year later.

Case 6 (N.H. 53466).—A business manager, aged 50, complaining of attacks of giddiness, deteriorating vision, and memory impairment.

For two years he had had attacks of unsteadiness, particularly when standing, which lasted only a few moments and then passed off leaving a slight frontal headache. Gradually the headaches became more severe. About six months before admission he noticed "difficulty with eyesight": this proved to be essentially difficulty in reading and writing. For the same period, his memory for recent events had become worse, his ability to do mental arithmetic deteriorated, and he had occasional feelings of "clumsiness" in his right leg. He had not had any difficulty in dressing or performing other tasks, nor had he suffered any topographical disturbance. His wife stated that in conversation he tended to "say the last part of the sentence first."

Neurological examination revealed a right homonymous hemianopia, with visual acuity 6/36 corrected in the remaining half-field on the right: in the left eye there was a lens opacity, and objects could only be perceived at one foot. There was slight inco-ordination of rapid movements in the right limbs, and occasional inattention on the right to bilateral simultaneous stimuli, but otherwise no somatic disability.

Psychological testing placed his premorbid intelligence in the superior range (Bellevue vocabulary: 33). He was mildly dysphasic, but understood and responded adequately to questions; his verbal reasoning was moderately impaired (Bellevue similarities: 7) and his arithmetical ability was practically non-existent. He passed Weigl's sorting test, though with difficulty: digit span was 5.

He showed marked impairment on *visual-constructive tasks:* he was unable to copy any of the block designs from the cards, and only one from a model; he was unable to reproduce match stick patterns from memory, and copied them poorly; and his drawing of a bicycle was over-simplified and fragmentary.

There was no evidence of dyspraxia, nor of finger agnosia: his right-left discrimination was occasionally at fault. There was a suggestion of neglect of his right hand, and of the right side of drawings and designs. Spatial perception, on the other hand, appeared to be unimpaired: he counted scattered dots correctly: he represented horizontal and vertical co-ordinates correctly; and the orientation of writing, and of the framework of his drawings, etc., was satisfactory.

At operation a large vascular meningioma was found on the left side, originating from the dura over the occipital lobe and extending forward through cerebral tissue into the left lateral ventricle, compressing the posterior part of the parietal lobe against the dura. It was removed and a course of irradiation given, following which his psychological disabilities had almost disappeared. Ten months after admission he returned to his administrative work.

Case 7 (N.H. 69228).—A housewife, aged 59, with six months' history of difficulty in using her right hand, and deterioration of memory, concentration, reading and writing.

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Eighteen months earlier she had two focal attacks involving the right hand: she did not lose consciousness but was amnesic for the episodes. She was admitted but investigations were not conclusive. Since then she became more easily fatigued, and during the last six months had frequently dropped things from her right hand, and would lean to the right when walking. Her reading, writing and memory deteriorated over this time.

On neurological examination vision was J.1 (corrected) in both eyes, with a right homonymous attention defect but no hemianopia. There was ataxia of movement in all limbs, but more so on the right side. Tendon reflexes were hyperactive on both sides, and abdominal reflexes absent on the right. Joint-position sense, two point discrimination and stereognosis were impaired on the right side, as well as attention to pin-prick.

Psychological examination placed her premorbid intelligence in the average normal range (Bellevue vocabulary: 20), with no evidence of verbal intellectual impairment (Similarities score: 11). Her arithmetic was moderately impaired (raw score: 4) and digit span only 5 forwards and 3 reversed. She was mildly dysphasic, making a number of paraphasic errors, but comprehension and expression were not significantly impaired: in reading and writing she made a number of errors even with easy words. She was able to explain a single complex picture (Terman-Merrill "Telegraph Boy") but was unable to deal with series (Picture Arrangement score: 4).

Visual-constructive tasks showed the most severe impairment: she was able to copy only the first block design, being unable to do the second from the card or from a model (the difficulty was always in placing the last, the top right hand, block); she could copy only the simplest drawings and match stick patterns, and in the more complex ones showed gross over-simplification.

Otherwise she showed no executive disability, her right-left discrimination, on herself, was unsure, but otherwise she showed no evidence of spatial disability. The orientation of her writing and drawings was good; and on the Terman-Merrill cube counting test (M, *X*, 1) she made only two errors, both of which she corrected on recounting.

At operation a meningioma was found overlying the left parietal lobe, extending from the central sulcus to the posterior border of the angular gyrus. Following its removal there was a transient right hemiplegia, but she recovered from this and from her psychological disabilities.

Case 8 (N.H. 51896).—A 37-year-old woman, an aircraft instrument inspector, complaining of seizures for five years.

A *grand mal* seizure occurred, without warning, while she was at work five years previously, and since then she had others at irregular intervals, approximately one a month. She also had minor attacks in which speech was arrested, the right hand moved involuntarily, and she might perform a few purposeless actions. On one occasion she experienced a distinct sensation of her surroundings being unreal and unfamiliar. Following these attacks she was confused for a few minutes, but gradually recovered her orientation.

She had never noticed any difficulty in her work, in finding her way about, or in dressing. As the seizures were increasing in frequency, she was admitted for investigation.

Neurological examination revealed no abnormality, apart from an equivocal right plantar response noted shortly after a minor seizure. Vision was 6/20 on the right and 6/12 on the left, with no field defect. Left carotid arteriography and air encephalography showed no evidence of any abnormality. EEG records showed evidence of a progressive abnormality: the first, six months after her first seizure, was flat and featureless; the second, seven months before admission showed episodes

of generalized abnormal activity with higher voltages on the left, and also isolated sharp waves suggesting a focus in the left frontal region; in the third, four months before admission, the record "again shows a fairly severe left-sided abnormality, which on this occasion is temporal rather than frontal"; while the fourth, made after admission, showed an increase in the generalized disturbance, again of greater amplitude in the left temporal region, together with occasional independent discharges of sharp waves in the left temporo-parietal and temporo-occipital regions. She was discharged to be followed in the outpatient department.

Psychological testing showed a considerable degree of deterioration, from a previously bright normal level. While pictorial and verbal test scores (Bellevue equivalent scores) ranged from 9 to 14, her score on Block Designs was 5 and on Arithmetic 3. She had a mild degree of nominal and receptive dysphasia, made a number of spelling errors when writing, and had difficulty in sorting on Weigl's test.

On *visual-constructive tasks* she showed the most striking impairment: she was able to make only the first two block designs, and on subsequent ones generally started off well but had great difficulty in placing the last one or two blocks correctly. She was unable to construct a 4-pointed star with matchsticks unless the model was left before her, and even then had difficulty placing the matches; and she was unable to construct a swastika with eight matches even with the model before her. Her drawing of a bicycle was simplified and inaccurate.

On the other hand, she passed the cube-counting test (using the card); she passed both parts of the paper-cutting test; she made no errors in identifying her own or the examiner's right and left; and described correctly a complex picture.

III. Analysis of Disabilities

Associated disabilities are considered under the same headings as in our earlier papers: they are summarized in Table I.

TABLE I.—ASSOCIATED DISABILITIES

Case No.	1	2	3	4	5	6	7	8
Visual field defect	—	+	—	+	+	+	—	—
Unilateral neglect	—	—	—	—	—	+	—	—
Counting scattered objects	NT	—	—	—	—	—	—	—
Dressing disability	+	—	—	—	—	—	—	—
Deformation of co-ordinates	NT	—	—	—	—	—	NT	NT
Right-left disorientation	+	—	+	—	+	+	+	—
Topographical disorientation	—	+	—	—	—	—	—	—
Cube counting*	NT	—	—	(+)	—	NT	—	—
Paper cutting†	NT	NT	—	—	—	NT	NT	—
Abstraction deficit‡	+	+	+	NT	+	—	NT	+
General impairment	+	++	+	++	++	+	+	+

*Terman-Merrill Form L, *IX*, 1.
†Terman-Merrill Form M, *X*, 1.
‡Weigl's sorting test.

\+ disability.
— no disability.
NT not tested.

Visual field defects.—4 of the patients showed field defects, ranging from hemianopia and defective vision in one eye (Case 6) to quadrantic loss (Case 2): in the remaining 4 patients perimetry showed no restriction of the fields.

Unilateral neglect.—In only 1 patient (Case 6) was there a suggestion of neglect of one side of space, and this was by no means marked: he tended

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not to use his right hand on tasks usually done with both hands, and he commenced writing and drawing on the left side of the paper, not making use of the right side.

Counting scattered objects.—This was done accurately by all patients given the task.

Dressing disability.—There was evidence of difficulty in dressing himself in only 1 patient (Case 1).

Deformation of co-ordinates.—The 5 patients tested were all able to represent correctly the horizontal and vertical co-ordinates of space with a stick held in one hand, with the eyes open and closed (Lenz, 1944).

Right-left disorientation.—5 of the 8 patients made errors in distinguishing the right and left sides of their own bodies: these errors also extended to sides of the examiner's body. The remaining 3 patients made no errors, on themselves or on the examiner.

Topographical disorientation: Only 1 patient (Case 2) gave a history of loss of topographical memory, although this was more episodic than the disability noted in right-sided cases. He also made a considerable error of orientation in drawing a map.

Cube counting.—Of the 6 patients asked to count irregular piles of cubes, either drawn on a card or as solid models, only 1 (Case 4) made conspicuous errors, and this was largely on account of dyscalculic errors in adding columns of 2 and 3 cubes.

Paper cutting.—All of the 4 patients tested passed at least one part of this test.

Non-verbal abstraction.—On Weigl's sorting test, 5 of the 6 patients tested were unable to shift from one principle to another.

General impairment.—As estimated by comparison of their present test scores with their vocabulary scores, or with the level expected from their occupations, all patients showed a significant degree of deterioration and in three (Cases 2, 4 and 5) this was considered to be to a marked degree.

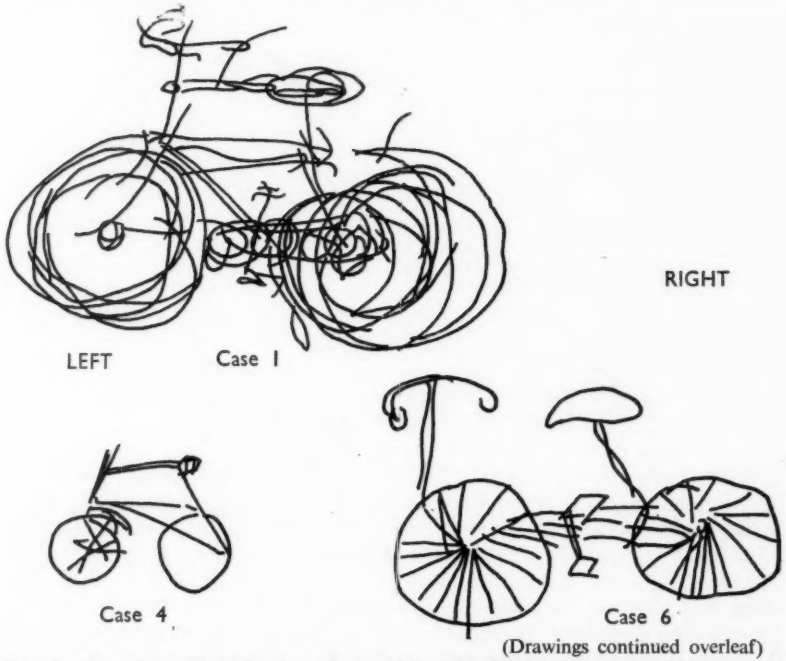
Comparison between the disabilities found in these patients and the disabilities found in association with right-sided lesions (cases reported by Paterson and Zangwill, 1944, 1945; McFie *et al.*, 1950; and Ettlinger *et al.*, 1957) shows a strikingly different distribution (Table II). Of the cases

TABLE II.—COMPARISON BETWEEN LEFT AND RIGHT SIDED LESIONS

	Left		*Right*	
	No. examined	*No. with disability*	*No. examined*	*No. with disability*
Unilateral neglect ..	8	1	21	14
Dressing disability ..	8	1	15	10
Cube counting	6	(1)	7	6
Paper cutting	4	0	10	9
Topographical loss ..	8	1	18	9
Right-left discrimination	8	5	21	0
Weigl's sorting	6	5	16	1

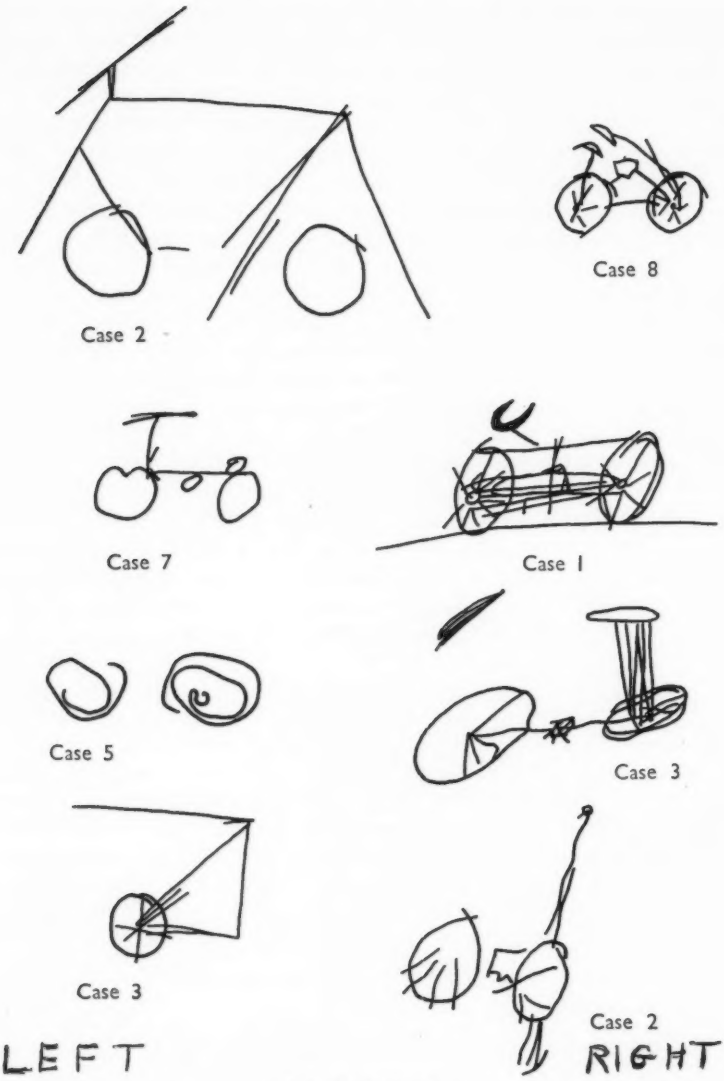
with right-sided lesions, the majority showed unilateral neglect and dressing disability, and also failed tests which call for spatial analysis; nearly half had trouble with topographical orientation; but none showed right-left disorientation on their own bodies, and only one was unable to sort both ways on Weigl's test. Examination of the reports shows that general intellectual impairment in these cases was on the whole absent or slight. In the patients with left-sided lesions, on the other hand, few show unilateral neglect, dressing disability, failure on spatial tests or topographical disorientation, while the majority show right-left disorientation on themselves and are unable to do the abstraction test; and there is in all cases a moderate or marked degree of general impairment.

There are also clear differences between the performances of the two groups on drawing and construction tests. Fig. 2 shows the efforts of patients from each group at drawing a bicycle from memory. While the drawings of the right-sided group represent many of the parts of the machine, they tend to be placed inaccurately in spatial relationship to other parts, the ultimate dissolution being a kind of exploded diagram (cf. the "piecemeal approach" of Paterson and Zangwill, 1944). The drawings of the left-sided group tend to preserve an accurate spatial relation-



(Drawings continued overleaf)

FIG. 2.—Drawings of a bicycle. Cases with right-sided lesions from McFie *et al.* (1950).



(Fig. 2 continued)

ship, but show a reduction in the parts represented, and ultimately a grossly over-simplified machine (an exception to this is seen in the bicyle drawn by Case 1: by occupation an artist, he was bewildered at his inability to make a correct drawing, and drew repeated lines in an effort to improve

his production). In their behaviour too these patients show differences, the right-sided cases drawing fairly energetically and often adding more strokes in an effort to make the picture correct, while the left-sided cases draw slowly, putting the few parts in with apparent difficulty.

Similar differences are found in other constructional tasks. Reproducing a four-pointed star with matchsticks (fig. 3) the right-sided patients

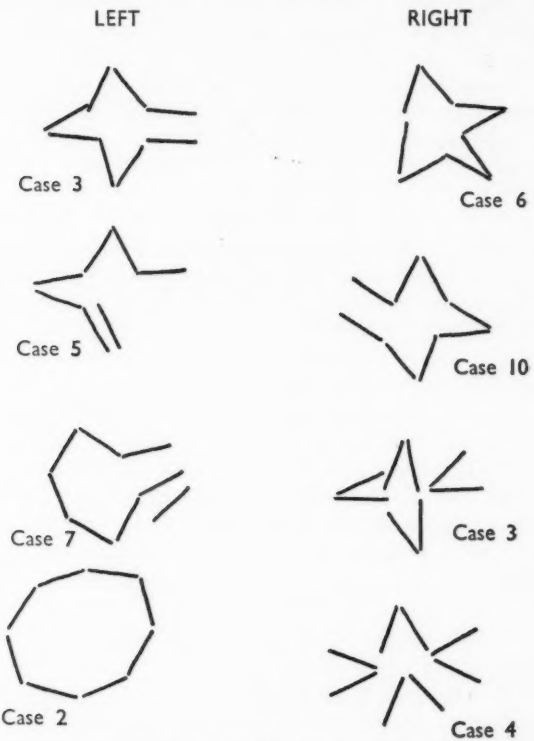


FIG. 3.—Attempts at constructing a four-pointed star with matchsticks. Cases with right-sided lesions from Ettlinger *et al.* (1957).

move the matches about a great deal, but have difficulty in representing any coherent structure; while left-sided patients place the matches slowly and carefully, and often arrive at a simplified figure which is coherent but is no longer a star. In copying Kohs' block designs, the right-sided patients may fail to orient any of the blocks correctly, and may even lose the simple square outline of the design (an excellent example is reproduced by Critchley, 1953, p. 183, fig. 91), while the left-sided patients may be able to reproduce the design all except for the last block, which seems to cause

great difficulty, and at least they preserve the square outline of the group of blocks.

In conclusion, the analysis indicates that the visual-constructive disabilities found in our cases with left-sided lesions are qualitatively different from those found with right-sided lesions, and are associated with a different pattern of deficits. Evidence of disturbance of spatial perception is absent or slight, and associated disabilities dependent upon a large spatial element, such as dressing disability and topographical disorientation, are rare. On the other hand, evidence of intellectual impairment in other fields is more common, and the constructional disability appears to involve a difficulty in copying some other aspect of a design than its purely spatial relationships, as well as some difficulty in actual manipulation of the components.

IV. Discussion

As in our series of patients with right-sided lesions, the occurrence of visual field defect is not invariable (it was found in only half the present group) and cannot be held responsible for the disturbances of construction. Unilateral neglect, whether of the patient's limbs or of extrapersonal space, was found in only one of the present series, in contrast with the majority of our right-sided cases: a similar distribution, in favour of cases with right-sided lesions, was found in the groups presented by Hêcaen *et al.* (1953) and by Arseni *et al.* (1958). Even in the series with right-sided lesions, however, we argued (Ettlinger *et al.*, 1957) that our "findings disprove the contention that visual-constructive disorder is wholly referable to unilateral neglect—or to a defect of 'morphosynthesis' presumed to underlie it"; and in the present series, it is even more apparent that the constructional disability cannot be attributed to "amorphosynthesis" as described by Denny-Brown *et al.* (1952, 1954).

Apart from the different types of breakdown on constructional tasks, the outstanding difference between the groups with left and right sided lesions is in the associated manifestations of *conceptual spatial* impairment and of other forms of *intellectual* impairment. Failure on tests requiring a relatively small amount of manipulation, in contrast to considerable understanding of spatial properties, was almost invariable in the right-sided series, but rarely encountered in the left-sided group. The paper-cutting test requires a minimum amount of drawing ability, and was passed by all those tested in the present series, but was failed by all except one of those with right-sided lesions. The cube-counting test calls for no manipulation on the part of the patient: in the present series, one patient was unable to produce the correct answers, a failure attributable largely to acalculia, which made it impossible for him to add up the numbers of cubes correctly. The occurrence of topographical disorientation, in the sense of getting lost in a familiar environment, parallels the occurrence of

other conceptual spatial deficits: it was noted in half the patients with right-sided lesions, but in only one of the left-sided group.

Dressing disability showed a similar distribution, being in evidence in half of the right-sided group, but in only one of the left-sided group. We should emphasize that by "dressing disability" we imply the same disturbance as that described in patients with right cerebral lesions by Brain (1941) as "apraxia for dressing." These patients made mistakes of orientation in putting on their clothes, e.g. trying to put them on upside-down or back-to-front: this is not the same disability as that described as "apraxia for dressing" by Denny-Brown *et al.* (1952, 1954), which was essentially a failure to dress the neglected half of the body.

The one disability which might, *a priori*, be thought to be related to disintegration of spatial concepts, but does not in fact appear to be so, is the failure of right-left discrimination on the patient himself. This was found in none of the earlier series, but was present in 5 of the present group. Its occurrence with left parietal lesions is of course well known, and constitutes an integral feature of Gerstmann's syndrome; but it may be of some theoretical interest to note that this evident disorder of personal body-scheme is not related to disturbance of appreciation of extrapersonal space.

In fields of intellectual function other than those involving spatial concepts, the patients with left-sided lesions showed consistently greater deficits than those with right-sided lesions. Some degree of language impairment was invariable; dyscalculia was common; and failure on a non-verbal abstraction test was seen in all but one of the present group, as opposed to one only of the right-sided series. 2 of the present group showed some dyspraxia of "lower" type; 2 were unable to interpret a complex picture ("Simultanagnosie"); and the 2 tested on Raven's Matrices did poorly. This constellation of deficits is not uncommon with left parietal lesions: in Schiller's (1947) series of 46 cases with left hemisphere gunshot wounds, intellectual deficits were most frequently associated with post-central lesions; of 58 cases with localized lesions, McFie and Piercy (1952*b*) found a significant degree of impairment on a number of intellectual tests in the left parietal group; and the same authors (1952*a*) found a significantly greater incidence of failure on Weigl's sorting test with left-sided lesions, of which the majority were in the parietal lobe. In the series of parietal cases analysed by Arseni *et al.* (1958) there are fewer patients with left-sided lesions: the authors state that a number of left-sided cases had to be excluded on account of massive aphasia or general impairment which made precise examination impossible. There is no suggestion, from any comparative series, that the degree of constructional disability parallels the extent of intellectual impairment.

The common feature, by intention, of our series with left and with right sided lesions is failure on visual-constructive tasks, but even in this narrow

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field differences in performances are evident (figs. 2 and 3). The disintegration of constructions and drawings in cases of spatial agnosia has already been amply described: in contrast, the performances of the left-sided group show difficulty, restriction, and retardation of a kind which corresponds closely to the description of constructional apraxia (cf. Mayer-Gross, 1935, 1936*a*, *b*). These disabilities parallel the disturbances in drawing noted by Head (1926) in some of his aphasic patients: "capacity to draw from a simple model . . . may be profoundly reduced if as with semantic aphasia the main defects depend on inability to appreciate the general meaning of a situation" (p. 360); and drawing a ground plan, drawing spontaneously, and drawing from memory were also impaired in patients with semantic aphasia, all of whom had sustained parietal or parieto-occipital injuries. 3 of the aphasics described by Weisenburg and McBride (1935) manifested gross disturbances of constructive performance; and of one in particular they observed that the disability "does not involve the simple reproduction of spatial figures but the production of these, and in the more complex language processes where the difficulty is evidently similar in nature, it is clear that the essential disorder is not spatial but constructive." A distinction between types of breakdown in construction has been noted by Duensing (1953), who did not ascribe the differences to side of lesion, but rather to consequences of bilateral lesions (spatial disintegration) or unilateral ("apraxic" type). Most authors, however (e.g. Hécaen *et al.*, 1953) have not drawn attention to these differences in the nature of the constructional disability; although Critchley (1953, p. 194) distinguishes between right and left parietal *agraphia*, the former being characterized by defects of arrangement, while the latter involves defects of language.

It has not been our purpose to attempt an analysis of constructional apraxia: the efficiency of different aspects of perception and execution was not examined in sufficient detail in our patients, nor were intellectual functions studied in sufficient detail to enable the relative influence of general impairment and of circumscribed disability to be assessed. Our final observation is on the subject of localization of the lesion, which in our patients has been consistently in the posterior parietal region. While the majority were tumours, in one patient (Case 8), in whom the syndrome was no less marked than in the others, the only abnormality found was a focal disturbance of electrical function. As we have noted, the majority of examples of constructional apraxia described have been in cases of generalized dementia, in whom the lesion must be presumed to be widespread: the disability has been ascribed to the left parietal region largely on account of its coexistence with other dominant parietal symptoms such as those of Gerstmann's syndrome. From the point of view of detailed analysis, however, such cases are unsatisfactory, since on the one hand patients with dementia often show bizarre features which may not be con-

firmed in a series, and on the other, the extent of impairment due to degeneration of other parts of the cerebrum cannot be assessed. Confirmation of differences between left and right sided lesions, and fuller analysis of the nature of constructional apraxia, will therefore depend upon studies of patients with localized lesions, on the one hand (cf. Hêcaen and Piercy) of unselected cases showing the disability, and on the other of cases selected to emphasize the common features of the syndrome.

V. Summary

A group of 8 patients is described in whom a lesion in the left hemisphere was accompanied by a prominent degree of visual-constructive impairment. In contrast to previously described groups with right-sided lesions, the disability in this group was rarely associated with unilateral neglect, apraxia for dressing, or failure on tests involving spatial analysis, including topographical memory; but was frequently associated with right-left disorientation and general intellectual impairment, including failure on a sorting test, with which the groups with right-sided lesions had little difficulty. There are also qualitative differences in the nature of the visual-constructive breakdown between the groups with left-sided and right-sided lesions, the former showing more difficulty in manipulation and restriction of response.

It is suggested that the disability shown by the present group of patients corresponds to the classical description of *constructional apraxia*, and is essentially different from the disability associated with *spatial agnosia* found with right-sided lesions.

It is noted that the lesion in all the cases was in the posterior parietal region, and it is suggested that fuller analysis of the disability will depend upon examination of series with adequately localized lesions.

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APRAXIA OF GAIT: A CLINICO-PHYSIOLOGICAL STUDY[1]

BY

JOHN S. MEYER AND DAVID W. BARRON

THE purpose of this communication is to describe and analyse in clinico-physiological terms the disintegration of motor performance of gait that results from cerebral damage particularly in the region of the frontal lobes. Previous clinico-pathological studies will be reviewed which establish that lesions of the frontal lobe may result in such a disability of gait. The present study is not concerned with anatomical correlation since some of the cases reported here were suffering from diffuse cerebral disease. Our purpose is to show that the disordered use of the lower limbs in apraxia of gait may be differentiated from cerebellar disease by simple clinical tests.

After careful review of the literature, we have not been able to find an extensive study in the English language which considers this disorder of gait from the point of view of a motor (limb-kinetic) dyspraxia, although the question has been discussed in the Swiss and French literature by Gerstmann and Schilder (1926), van Bogaert and Martin (1929), and Delmas-Marsalet (1936). Recently Denny-Brown (1958), in a clinical review of all types of apraxia, has discussed the question of disorder of gait resulting from lesion of the frontal or parietal lobe. There is evidence that lesions of either or both of these regions may result in apraxia of gait, but in cases of parietal lobe damage, there is usually demonstrable sensory loss (Denny-Brown, 1958; Denny-Brown, Meyer and Horenstein, 1952).

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Since the first description by Bruns in 1892 of "ataxia of gait" associated with tumour of the frontal lobe, there have been numerous additional case reports. In the majority it was concluded that although the cause of the "cerebellar signs" was unknown, direct or indirect damage to the cerebellum was probably responsible. After reviewing our own clinical experience and comparing it with the reports of others in the literature, it appears that *apraxia* of gait has often been confused with cerebellar *ataxia* and the problem deserves further clinical study.

There is no experimental animal with an upright gait comparable to that of man nor with sufficient comprehension to permit testing for dyspraxia. Thus it seems evident that the question of whether or not the disorder of gait seen in some cases of cerebral disease is due to limb-kinetic dyspraxia can only be determined by careful study of the human subject. We believe the present account of 7 cases that have been studied in detail clinically for evidence of dyspraxia may shed light on the problem.

First, a brief summary of the literature pertaining to disorders of gait associated with cerebral lesions will be presented. Review of the numerous anatomical studies that have been published leaves little doubt that unilateral or bilateral lesions of the first and second convolutions of the frontal lobe may result in gross disturbance of gait. In most of the case reports where the lesion was demonstrated at necropsy or operation, the clinical studies were retrospective. Possibly this explains in part why there is disagreement concerning the signs that result from lesion of the frontal lobe and the nature of their production. In each of the 7 cases that will be described here, an attempt has been made to analyse the nature of the disturbance of gait in clinico-physiological terms. In our case material there has, as yet, been no confirmation of the lesion at necropsy, but in every instance, verification of the clinical impression of the site of the lesion has been provided by surgical, roentgenographic or electroencephalographic study (Table I). It is believed, however, that the detailed clinical observations reported here (with cinematographic records in 3 cases) permit certain conclusions regarding the nature of one type of gait disturbance that results from cerebral damage. An explanation is also offered for apparent discrepancies in the semeiology of "frontal ataxia" in cases that have been reported previously.

Review of the Literature

"*Frontal Ataxia*"

According to the German neurologist Bruns (1892), there were several authors including Oppenheim, Wernicke and Bernhardt who mentioned signs of ataxia similar to that seen in cerebellar disease in association with tumours of the frontal lobe prior to the appearance of his paper but he was the first to describe in detail the disturbance of gait and station that is sometimes seen with tumour of the frontal lobe and to offer confirmation

TABLE I

Case No.	*Diagnosis*	*How established*	*Gait disorder*
1	Hypertensive vascular disease. Stenosis right anterior and middle cerebral arteries	Arteriogram	Apraxia of both legs, more marked on left. Unable to walk unassisted
2	Frontal lobe atrophy secondary to paretic neurosyphilis, inactive	Pneumoencephalogram	Apraxia of both legs, more marked on left. Unable to walk unassisted
3	128 grammes parasagittal meningioma right frontal lobe	Surgical removal	Apraxia of both legs, greater on the left. Shuffling, hesitant gait
4	Atherosclerosis left internal carotid and anterior cerebral arteries	Arteriogram	Apraxia of both legs. Unable to walk unassisted
5	Metastatic carcinoma (cervix) right frontal lobe	Arteriogram. Biopsy of cervix	Apraxia of left leg, unable to walk unassisted
6	Hypertensive vascular disease, anterior cerebral artery insufficiency. Hypoventilation syndrome of obesity	Clinical, EEG and pulmonary function studies	Apraxia of both legs, slow in initiating gait, shuffling gait, difficulty in turning
7	Atherosclerotic occlusion left anterior cerebral artery, stenosis right anterior cerebral artery	Arteriogram	Apraxia of both legs, greater on left. Slow in initiating gait, wide based, shuffling, difficulty in turning

of the site of the lesion in 4 cases by necropsy. Duchenne (1864) in his discussion of the various forms of ataxia, makes no mention of "frontal ataxia." In two of Bruns' cases, the tumour was localized in the first and second frontal convolutions and in the other 2 cases, this area was involved together with more diffuse damage. Since then, numerous cases of "frontal ataxia" with autopsy have been reported in which lesions have been demonstrated in the mesial aspect of one or both frontal lobes anterior to the parasagittal portion of the precentral gyrus (electrical stimulation of which produces movement of the opposite lower limb).

Bruns was of the opinion that the differential diagnosis between frontal ataxia and cerebellar disease could be made during life by means of accompanying signs of disturbance of the frontal lobe such as hemiparesis, clouding of consciousness, euphoria and inappropriate response. He was not of the opinion that "ataxia" of frontal lobe origin was significantly different in its clinical manifestations from that seen with cerebellar disease. In discussing the possible cause of these signs, he mentioned that Wernicke was of the opinion that "frontal ataxia" was due to paralysis of the muscles of the trunk which he believed were controlled by the frontal lobe. Bruns himself considered that signs of ataxia in frontal lobe tumour were due to compression of the cerebellum resulting from displacement of the brain or possibly to interference with the fronto-ponto-cerebellar tract.

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In 1904, Collier mentioned that ataxia occurred in one of his cases of tumour of the frontal lobe as a false localizing sign. At necropsy, it was noted that brain swelling had resulted in compression and herniation of the cerebellar vermis and tonsils within the formen magnum. In this case, there appeared to be adequate local evidence in the posterior fossa to account for the cerebellar signs. Grainger Stewart, in 1906, described the fine action tremor that occurs in the upper and lower limbs on the same side as tumour of the frontal lobe. Clovis Vincent (1911) in a discussion of errors in localization of brain tumour emphasized that ataxia may be caused by certain frontal tumours, and if misinterpreted, the unwary surgeon may erroneously explore the posterior fossa. Two cases were described of frontal lobe tumour in which there was ataxia and a tendency to fall to the side opposite the tumour. Abnormal responses to labyrinthine stimulation were noted and nystagmus was present in one case. Vincent believed that frontal ataxia could be differentiated on clinical grounds from cerebellar ataxia since dysdiadokokinesia, dysmetria, dyssynergia and scanning speech were absent in frontal lobe lesions. He concluded that posterior and inferior displacement of the brain by tumour resulted in stretching of the eighth nerve causing ataxia of a labyrinthine type. In his first case this conclusion was justified since the ataxia was relieved by simple decompression rather than by removal of the tumour.

In 1917 and later in 1934, Gordon described observations in cases of ataxia due to expanding lesions of the frontal lobe (tumour, abscess, hæmorrhage) and described how they could be differentiated from cerebellar lesions. He emphasized that there was "dissociation" of the signs (e.g. ataxia may occur on the same side in which the tendon-jerks are increased and hypotonia may occur on the side opposite the ataxic limbs). He also failed to find a positive rebound test described by Holmes and Stewart or the pendulous knee-jerks described by André Thomas. He mentioned that Engert and Hoff had noted that patients with cerebellar disease are incapable of walking on all fours (like four-footed animals) whereas patients with frontal lobe lesions are able to do this. Gordon concluded that the frontal lobe is a centre for equilibrium and orientation and that damage to the fronto-ponto-cerebellar tract results in ataxia.

Puusepp (1927) in his book on tumours of the brain observed that most of those which were deep-seated and of small size were associated with disturbances of equilibrium. He concluded that the ataxia is due to damage to the fronto-ponto-cerebellar pathways and that if the tumour lay between the frontal lobes, the disturbance of gait was bilateral and more pronounced. He believed that the nystagmus which occurred in most of his patients was due to intracranial pressure. Purves-Stewart (1927) made observations similar to those of Vincent, namely, that ataxia occurs in prefrontal tumours but is not associated with dysmetria or dyssynergia. He was unable to decide whether these signs were due to

backward displacement of the cerebellum or disturbance of the crossed fronto-cerebellar paths.

Sachs (1927) in a discussion of frontal lobe lesions mentioned unilateral tremor which may occur on the same side or on the side opposite to the lesion and resembled the tremor described by Stewart. Dysdiadokokinesia was present in one of his cases (opposite the lesion) but no mention of ataxia was made. Grant (1928) reported a series of cases of frontal lobe tumours collected from Cushing's service in which the diagnosis of posterior fossa tumour had been made in error and the cerebellum explored. He believed that the most likely explanation was displacement of the brain with compression of the cerebellum.

In 1931, Hare published a detailed study of the significance of cerebellar symptoms in tumours of the frontal lobes. He reviewed previous reports and discussed the anatomy of the fronto-ponto-cerebellar pathway. As a result of clinical and autopsy studies of 5 of his own cases of frontal lobe tumour, Hare concluded that the cerebellar symptoms were the result of involvement of the fronto-ponto-cerebellar pathways. He believed that if only one fronto-ponto-cerebellar tract is diseased, that of the other side might compensate and cerebellar symptoms not result, but if both pathways are involved, compensation fails and cerebellar signs result, which may be bilateral, on the same side as the neoplasm or on the opposite side. He concluded that cerebellar symptoms only result if there is involvement by tumour of both frontal lobes. The latter conclusion is not supported by anatomical studies reported by others in which there was strictly unilateral frontal lobe disease with signs of "ataxia."

Barré (1936) expressed the belief that disease of the frontal lobe did not give rise to ataxia and that the term "frontal ataxia" should be discontinued. He disagreed with Gerstmann and Schilder (1926) and van Bogaert and Martin (1929) that there was such an entity as apraxia of gait. He cited his own experience with four cases (all with tumour of the third ventricle) and emphasized the retropulsion and "inattention" of patients with frontal lobe disease. He stated that he agreed with the view of Muskens that the "ataxia" seen in frontal lobe disease is due to damage to the globus pallidum or compression of the red nucleus and its pathways. In view of the recent, widespread use of chemopallidectomy in the treatment of involuntary movements, it seems unlikely that damage to the pallidum produces severe disturbance of gait. One year later, Austregesilo and Fortes (1936) reviewed the problem on the basis of experimental studies and suggested the ungainly term "frontal dysequilibrium and ataxia" since they obtained disordered gait, change in labyrinthine response and tonic deviation of the head and neck following frontal lesions in the dog. They believed that disorder of the labyrinthine response was important in the production of dysequilibrium.

In the same year (1936) Frazier reviewed the symptoms in 105 verified

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cases of tumour involving the frontal lobe alone. In many of his cases the tumour involved only one frontal lobe, and yet contrary to the conclusions of Hare (1931) contralateral "ataxia" was present. Frazier concluded that there are two types of ataxia in association with frontal lobe tumours, the first appears early, is unilateral (often contralateral) and appears to result from involvement of the frontopontile pathway. The second is bilateral, appears in the terminal stages of tumour and is due to pressure on the cerebellum from displacement of the contents of the middle cranial fossa. This conclusion, that there are two types of "ataxia" in frontal lobe lesions, is shared by Bing (1926, 1956) who also described differences between "frontal ataxia" and cerebellar ataxia. In unilateral lesions, the patient, in walking forward, advances the contralateral foot with striking awkwardness, setting it down too far laterally or in front of the other foot. Dysmetria and dysdiadokokinesia are usually absent. As pointed out by Bruns, when past-pointing is present, it is open to voluntary compensation. In addition, Bing described disorders which are foreign to cerebellar lesions such as paucity of movement (hypokinesis) reminiscent of Parkinson's disease. Occasionally a patient with "frontal ataxia" who is trying to stand still will take short, tripping steps backward and in advanced cases, the patient can neither stand nor walk (astasia-abasia). He mentioned that a tonic plantar reflex assists in differential diagnosis.

Apraxia of Gait

In 1916, Gerstmann reported 6 cases of war-wounds involving the frontal lobes which resulted in disturbance of gait which he believed was due to damage to the fronto-ponto-cerebellar tract. He mentioned in this account that there was no paralysis or sensory loss in the lower extremities and offered convincing evidence that the disorder was not due to diaschisis or increased intracranial pressure. However, at this time he did not discuss the possibility that the disorder of gait was due to dyspraxia.

No mention is made of apraxia of gait in the classic monographs on the subject of apraxia by Wilson (1908) and Liepmann (1914). The first discussion of the possibility that the gait disturbance occurring in frontal lesions is due to apraxia of the lower limbs was published by Gerstmann and Schilder in 1926. These authors quote an earlier case published by Hartmann in 1907 in which a tumour of the corpus callosum and frontal lobes was associated with apraxia of the trunk and legs, but in reviewing Hartmann's paper, this case is unsatisfactory since the involvement by tumour was extensive and the discussion is concerned with the general problem of apraxia rather than the disturbance of gait. Gerstmann and Schilder described 2 cases in which the disturbance in gait was clearly due to apraxia of the lower extremities. In 1 case, the location was confirmed at necropsy where a glioma was found in the frontal lobe.

In 1929 van Bogaert and Martin contributed a masterly discussion on

the subject of apraxia of gait. They emphasized that practically all of the reported cases of "frontal ataxia" had been inadequately studied clinically. They criticized the term "frontal ataxia" which is confusing and suggested the use of the term "frontal dysequilibrium," a syndrome which they believed merits careful clinical study, and, in their opinion, was due to an apraxia of the lower limbs. These authors described 2 cases with lesions of the frontal lobes verified at autopsy in which there was clumsiness in the use of the lower limbs in walking. Although occasionally hypermetria and dysdiadokokinesis were present, the movements were slow, poorly performed and variable from one moment to the next. The disorder of the lower limbs could not be accounted for by any motor or sensory disturbance. They pointed out that even when assisted, the patient had great difficulty in walking, particularly forwards. The feet were hesitant, stuck to the ground, and tended to scrape the ground when any attempt to walk was made. In addition, the patients were unable to make pedalling movements of the feet on command. van Bogaert and Martin refer to the question originally raised by Gerstmann as to whether the disorder is due to damage to the frontal lobe or to the corpus callosum. They concluded that it is due to frontal lobe disease. More recent studies have shown that surgical section of the corpus callosum in man does not result in apraxia or gait disturbance (Akelaitis *et al.*, 1942, 1944).

Perhaps the most complete discussion available at the present time regarding the question of disturbance of gait and equilibrium resulting from damage to the frontal lobe is that published by Delmas-Marsalet in 1936. He reviewed both experimental and clinical studies and pointed out that while the claims of many authors that disturbance of equilibrium in frontal lobe tumours may be due to pressure on the labyrinth or compression of the cerebellum in some instances, this explanation does not account for those cases with symptoms due to vascular lesion or gun-shot wound of the frontal lobe where there is no increase of intracranial pressure. In some cases he believed that the disturbance of gait was due to apraxia while in others he considered the difficulty might be due to spatial disorientation, disorder of "postural image" and a false impression of displacement of the body. The latter views are purely theoretical, however, since it is generally agreed that damage to the parietal rather than the frontal lobe gives rise to such disorders of perception.

Goldstein (1942) mentioned numerous disorders of equilibrium associated with lesions of the frontal lobe in his extensive study of brain-injured patients. Akinesis, bradykinesis, catalepsy and rarely catatonic stupor were prominent in patients with bilateral frontal lobe lesions. Tilting of the body away from the side of the lesion occurred while the arms and occasionally the legs showed heterolateral deviation. Disturbances of co-ordination of the entire body in all movements was prominent with bilateral involvement of the frontal lobes. Such symptoms were especially

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prominent with lesions located in the premotor area of the first and second frontal convolutions.

In his detailed monograph on agnosia, apraxia and aphasia, Nielsen (1946) has little to say on the subject of apraxia of gait and of the lower extremities. He quotes the conclusion of Sittig that damage to the corpus callosum produces apraxia of the trunk and lower extremities. However, in the light of surgical studies that have already been discussed, this conclusion is no longer tenable.

Klein and Mayer-Gross (1957) in their book on the examination of patients with organic cerebral disease have outlined an excellent series of tests for dyspraxia of the trunk and legs. Whenever possible, we have applied these tests to the patients reported here. The tests include turning from the prone to the supine position, sitting up from the lying position, bending the trunk, walking, running, hopping, knocking with the heel on the floor, standing to attention, turning, making a circle or number with each leg or kicking a ball. They comment that these actions are highly automatized, composite movements and in dyspractic patients, the automatic sequence is lost, the action is carried out piecemeal and every part of the act seems to have become a problem in performance. When walking, the patient may step with one foot forward, then hesitate, make another step forward with the same foot and come to a standstill. He may lift the leg without advancing or appear to be unable to lift the foot from the ground (floor-bound).

Recently Denny-Brown (1958) has contributed a valuable and provocative appraisal of the various types of apraxia. In the patient with frontal lobe lesion, he found evidence that release of the grasp reflex interfered with motor performance. When such a patient attempts to write the hand stiffens and appears to stick to the paper. When severe, this results in apraxia of writing. If the foot grasp is present, placing the affected foot on the floor results in stiffening of the lower limb which becomes glued to the floor so that steps are made only with great difficulty, and when made, are but a brief shuffle. Only when the heel is at last raised from the floor can the foot be lifted and a complete step be made. Even then the toe fails to extend completely as the foot is advanced; yet the limb can be moved freely in space. Denny-Brown concluded that in mesially placed lesion of the frontal lobe, all types of movement were interfered with by a mechanism that in all its essentials was exemplified by the instinctive grasp, namely, an abnormal persistence of posture which also accounts for the perseveration so common in lesions of the frontal lobe. In clinico-physiological terms, he classifies the apraxias resulting from frontal lobe lesions as "magnetic apraxias," to contrast them from those arising from disease of the parietal lobe which he terms "repellent apraxias."

Clinical Observations

The 7 cases that form the material that we have studied have been tabulated in Table I according to diagnosis, method of confirmation of the diagnosis and the type of disorder of gait. Brief summaries of each of the 7 cases will be presented.

Case 1 (Detroit Receiving Hospital No. 242236).—A 71-year-old white male retired labourer was admitted to hospital because of difficulty in gait and clumsiness of the left leg resulting in several falls. Impaired memory, confusion and incontinence had been noted by his friends and relatives. He was known to have suffered from hypertension and "failing heart" for several years. Three days prior to admission, he had found himself unable to walk more than a few feet without falling which he blamed on stiffness in the legs and knees. Ten years prior to admission, he had suffered from venereal disease (presumably syphilis) for which he had been treated with injections for several months.

On examination, the temperature was 98·6° F., pulse was 80 per minute and regular, blood pressure was 208/100 and respirations were 20 per minute. He was unkempt with an expressionless face except for a tendency to pathological crying. The heart was moderately enlarged without murmurs and a few râles were heard at the base of the lungs on auscultation. The chest was emphysematous. There were numerous bruises over the knees and ankles. He spoke slowly in answer to questions but was co-operative, alert and oriented. He lay quietly in bed with the head flexed as though lying on an invisible pillow. Judgment and insight were poor with a deficit in abstract thinking. He could not subtract 7 from 100 or reverse 3 digits, but correctly repeated 6 digits forwards. A "concrete" type of interpretation of proverbs was given. For example, when asked the meaning of "It is the last straw that breaks the camel's back" he replied, "the straw is too heavy" (Goldstein, 1942). The optic discs and visual fields were normal but there was moderate arteriosclerotic retinopathy with recent and old perivascular exudates. The pupils and eye movements were not remarkable and no nystagmus was present. A light tap with the finger on the glabella produced blepharospasm (Myerson's sign). There was fine tremor of the outstretched hands and fingers having an amplitude of 1/2 cm. and a rate of 5 beats per second. All movements were slow but no weakness was evident. Plastic rigidity was present in all four extremities and gegenhalten was present in the lower extremities.

In attempting to walk, there was difficulty almost to the point of inability in initiation of the first step with either foot (fig. 1A and B). He shuffled the foot a few centimetres, stopped, staggered and clutched the examiner for support. The foot in attempting gait scraped the ground a few centimetres as though glued to the floor. The disability was more marked in the right leg and presented the picture aptly termed the "slipping clutch syndrome" (Denny-Brown, 1958). In attempting to walk, he tended to fall backward or to either side. Turning to either side was impossible unless he was supported by the examiner, in which case the foot on the side to which he turned remained rooted to the ground and occasionally there was extension of the great toe (fig. 1C). The station was abnormal, he stood or attempted to walk with both feet set one and a half feet apart.

Cinematographic records were made of his gait together with tests to demonstrate the dyspraxia present in the arms as well as the legs. Movements of the trunk were normal, although he bent forward or to the side slowly. He had considerable difficulty in arising from the sitting to the standing position and required assistance since he would often topple back into the chair or to the floor. In standing, he held his hands widely to balance himself and occasionally veered backward or to

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the right. When he was told to execute special movements with the foot in the air, he was unable to do so with either foot. In attempting such movements, there would be a delay of 10–30 seconds before any movement of the legs occurred at all. For example, when asked to touch the examiner's finger with either foot, after a delay he would lift it slowly a few inches from the ground where it would remain suspended (fig. 1E and F). He was unable to make kicking movements, perform the heel to shin test or draw a circle with his feet. When told to touch his finger to his nose, he did so slowly and a fine action tremor was evident. We wish to emphasize that the slow, hesitant manner in initiating these movements, the tremor, difficulty in placing his hand on his nose and inability to perform any rapid, alternating movements with the limbs, gave a superficial but spurious resemblance to the terminal tremor, dysmetria and dysdiadokokinesis seen in cerebellar disease. There was no dysphasia and he was able to read and write slowly. A sucking reflex was present (fig. 1D) and an instinctive grasp reflex was present in both hands. A grasp reflex of the foot could not be elicited. The tendon-jerks, including the finger-jerks, were generally increased and both plantar reflexes were extensor. Unilateral and bilateral sensory stimulation (pin-prick, light touch, vibration, temperature) were correctly identified and position sense was present in the toes, feet and fingers. The station was not made worse by closing the eyes (Romberg's sign as defined by Denny-Brown, 1946). Compression of either the left or right carotid artery for ten seconds produced a left-sided seizure with temporary amnesia.

Lumbar puncture revealed crystal clear fluid with an initial pressure equivalent to 60 mm. of water and a final pressure of 30 mm. after removal of 10 ml. No cells were noted in the spinal fluid and the Kline test was negative. The total protein was 55 mg. per cent. Serum lipids were 600 mg. per cent, cholesterol 273 mg. per cent and blood hæmoglobin and white count were normal. The quantitative blood Kahn test for syphilis was weakly positive (interpreted as compatible with inactive syphilis). Blood urea nitrogen was 24 mg. per cent and fasting blood sugar was 118 mg. per cent. Urine examination was normal. Electrocardiogram showed depression of the "T" wave compatible with myocardial ischæmia and routine electroencephalogram was within normal limits. Skull roentgenograms were normal.

Clinical diagnoses of atherosclerotic occlusion of both anterior cerebral arteries and inactive (serological) syphilis were made. Right carotid arteriography was performed by Dr. Sheila Sheehan which showed irregular calibre with severe stenosis of both the right middle and anterior cerebral arteries (fig. 5B) on three separate injections of the contrast medium.[1] The parasellar portion of the internal carotid artery also showed irregularity of the lumen. Attempts were made to re-educate the patient in gait with the use of a mechanical walker mounted on wheels. After five weeks he was discharged to a convalescent home without significant improvement.

Case 2 (Detroit Receiving Hospital No. 52936).—A 68-year-old Negro male, known to be suffering from syphilis since 1943, was admitted to the Neurological Service for investigation of difficulty in gait and seizures. In 1943, he had been discharged from his employment because of generalized seizures and admitted to another hospital where a diagnosis of syphilis (type not specified) was confirmed by a positive serological test. Records concerning the clinical examination and type of treatment that he received at that time unfortunately are not available, but in retro-

[1] The radiopaque contrast medium used for all the arteriograms in this study has been 60 per cent Renografin (methylglucamine salt of 3, 5-diacetylamino-2, 4, 6-triiodobenzoic acid) manufactured by E. R. Squibb and Sons, New York. This is less irritating than Diodrast which we consider contra-indicated in patients with cerebrovascular disease.

spect, he appears to have been treated for the paretic type of neurosyphilis. He first visited the medical out-patient clinic of the Detroit Receiving Hospital in 1954 for the treatment of generalized seizure. At that time, the positive physical findings included: disorientation, confabulatory dementia, drowsiness, mask-like facies, catatonia, Argyll-Robertson pupils, slow, shuffling gait with absence of associated movements of the arms, cogwheel rigidity, slight right hemiparesis and diminished tendon-jerks in the right arm. Blood serological test for syphilis was positive but the Kline test was negative and no cells were present in the cerebrospinal fluid. At that time he was admitted to hospital and treated with 5 million units of penicillin and a course of bismuth and neoarsphenamine.

The seizures were controlled with dilantin and phenobarbital and after discharge, he was assisted to the out-patient clinic at intervals of three months. His wife and a close friend who assisted him to the clinic stated that "his memory is very poor, he does not seem interested in anything and talks very little."

He was first examined in the Neurology Clinic in March 1958. Review of his blood serological test for syphilis since 1954 showed that the Kahn test had remained strongly positive. He was, therefore, readmitted to the Neurology Ward for re-evaluation.

On examination, the patient sat by his bedside for hours at a time with little spontaneous movement. He remained in catatonic attitudes (fig. 3A) but when spoken to, he readily understood what was said to him and replied slowly but in a readily comprehensible manner without dysarthria or dysphasia. He followed simple instructions but was occasionally incontinent. Blood pressure was 150/90, temperature and pulse were normal. A loud systolic murmur was present at the apex of the heart and there was pitting œdema of the ankles. In other respects the general examination was unremarkable.

He was disoriented to time but not to place or person. The visual fields and fundi were normal. The pupils were irregular and failed to react to light but did so in accommodation. There was a fine, rapid tremor of the tongue and an expressionless face. Hypokinesis and plastic rigidity were present in all four extremities but there was no loss of strength. A sucking reflex was present but a grasp reflex was not present in the hands or feet. The tendon-jerks were slightly increased in the right arm but both plantar reflexes were flexor. Detailed sensory examination revealed no defect.

When asked to write his name he showed apraxia of writing. He held the pen too high (fig. 3B) and there was perseveration of letters of parts of words. For example, when asked to write or copy his first name "Cass" he placed the pen to the paper, made several small scratches, and after considerable delay, wrote a "C" which he then repeated several times (fig. 3D). When asked to write his last name (Bailey) he wrote "BaBaBaBailll," and when told to write "It is a nice day, today" he wrote "itititit."

Catatonia (in the sense of motor perseveration of posture) was demonstrable in his spontaneous movements or if either hand was placed above his head. His hands would then drift downward over a measured interval of 3–5 minutes (fig. 3A). When asked to perform the finger to nose test with either hand, he would slowly place his finger on that of the examiner's where it would remain as though stuck to it (fig. 3C). When the examiner placed the patient's hand on his nose, it would tend to remain there (perseveration of posture). He was unable to place his left thumb on his right ear but instead would hold up his hand and extend his thumb slowly and abandon the test. Dyspraxia was present in both feet. When told to lift up either foot he did so slowly and was unable to touch the examiner's finger or cross his legs.

He was able to rise from the sitting to the standing position unaided, but he moved slowly and hesitantly holding on to the arms of the chair. The trunk was held

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rigidly but he could bend his trunk on command. Both station and gait were wide-based. When unsupported, he was able to stand, although he was apprehensive that he might fall. He was unable to initiate gait without help and any movement he attempted to make resulted in a series of shuffles and then he would reach out for support with the hands. There was extreme slowness and difficulty in initiating gait with either foot when supported, and when propelled forward by the examiner, he was unable to step out and tended to fall forward and reach out for support (fig. 2A). When he attempted to step out with either leg, the foot remained rooted to the ground (fig. 2B and C) but after a delay, he finally was able to raise one foot up only to take a small, shuffling step (fig. 2D). The feet were held wide apart, and the hands were used to aid in maintaining his precarious balance (fig. 2B and C). Once gait was initiated, he was able to shuffle along with wide-based short steps, but if he stopped, the whole cycle had to be repeated. He was unable to turn to either side on command.

Lumbar puncture revealed clear cerebrospinal fluid with normal pressure, no cells, and a total protein of 57 mg. per cent. The colloidal gold and Kline test for syphilis were negative. In spite of the negative spinal fluid serology, he was treated with 12 units of penicillin. During hospitalization, several *grand mal* seizures were seen, which began with rotation of the eyes to the left. Following each seizure, he became stuporous for several hours. These seizures were controlled by increasing his anti-convulsive medication. Bilateral carotid arteriograms and pneumoencephalograms were performed by Dr. Sheila Sheehan. The arteriograms showed normal appearing carotid, middle and anterior cerebral arteries and their branches. The vessels were not displaced except that the pericallosal branch of the anterior cerebral artery appeared to be pushed upward by enlargement of the frontal horns of the lateral ventricles. Pneumoencephalogram showed considerable dilatation of the lateral ventricles, slightly greater on the left, with maximal enlargement in both frontal horns (fig. 5A). There was no displacement of the ventricles.

Additional laboratory data were as follows: Skull roentgenogram negative, Kahn test on peripheral blood positive (4+), serum cholesterol 292 mg. per cent, serum lipids 917 mg. per cent, blood glucose, hæmatocrit, blood count, blood urea nitrogen, alkaline phosphatase and bilirubin all within normal limits.

The final clinical diagnosis was General Paresis, inactive. The patient continues to be seen regularly in out-patient clinic and his status remains unchanged.

Case 3 (Detroit Receiving Hospital No. 316419).—A 51-year-old white male entered hospital with complaints of loss of memory for one year. One year before admission, his family, friends and co-workers noted that he seemed to tire easily and that his personality had changed. He became withdrawn, ate little and his judgment and memory were impaired. Six months before admission, he lost his employment because of poor work performance and became incontinent of urine. He had the desire to void but "could not get to the bathroom in time." His wife noted that he seemed nervous, smoked more than usual and appeared to have lost his balance. He moved slowly and stumbled and shuffled when he walked.

The patient himself complained that his balance was poor and getting worse. He stumbled over objects and had difficulty climbing stairs and mounting the curb on crossing the street. He was slow in dressing, tended to "stare off into space" and vomited after eating. The past medical history and family history were not relevant to his present complaints.

On examination, he was a well-developed white male whose spontaneous movements were slow and he had difficulty following commands. He tended to sit or stand in a stiff, rigid posture. He was slow in initiating gait, taking slow, shuffling steps, tending to lurch or fall to either side. The gait was not wide-based but he had

difficulty placing one foot in front of the other, in turning to either side and performing simple movements on command with the feet. Romberg's sign was not present. The blood pressure was 120/80 and pulse, respiration and temperature were normal. He was orientated but was only able to repeat two or three objects after one minute. He repeated five digits forward slowly but was unable to reverse four digits. He was able to subtract simple numbers correctly. Tests of insight, judgment and abstraction showed a considerable deficit with inappropriate comments, trends of suspicion and acute anxiety under test situations. He was unable to interpret simple proverbs. Cranial nerves showed no papillœdema or other abnormality except for slight central type of facial weakness on the left.

Strength in all four extremities was normal and he carried out tests of co-ordination slowly but correctly in the upper extremities. There was bilateral rigidity in all four extremities with gegenhalten and perseveration of posture in the legs. Occasionally there was a fine action tremor present in all four extremities, this tremor was distal, having an amplitude of 1 cm. and involving only the hands and feet. The rate was six cycles per second and it was noted by us that it was "more rapid than is seen in cerebellar tremor." The tendon-jerks were symmetrically increased with bilateral extensor plantar responses. Sucking reflexes and grasp reflexes of the hands and feet were not present. Sensation was normal except that vibration sense was decreased in the left toes. There was no sensory deficit on bilateral simultaneous stimulation and two point discrimination was intact.

Lumbar puncture revealed crystal clear cerebrospinal fluid with initial pressure of 180 mm. of water and final pressure of 80 mm. The total protein was 59 mg. per cent (normal values do not exceed 45 mg. per cent) and the Klein test, Pandy and colloidal gold were negative. Pneumoencephalogram showed a filling defect of the right lateral ventricle, enlargement of the left lateral ventricle with displacement of the frontal portion to the left and displacement of the pineal gland to the left. Right carotid arteriogram showed displacement of the anterior middle cerebral artery to the left and the callosomarginal and pericallosal branches were spread apart. A diffuse increase in small vessels was noted in the frontal region (fig. 5c). At operation, a right frontal craniotomy was performed by Dr. Harvey Gass and the frontal convolutions were noted to be flattened on the right. At a depth of 1 cm., a hard mass of tumour was exposed, dissected and removed. The tumour arose from the falx and weighed 128 grammes. Microscopic diagnosis was parasagittal meningioma, right frontal lobe. The patient has been examined repeatedly during the eight months following surgery. He has regained normal mentation, walks normally and has returned to work. There is now no neurological deficit.

Case 4 (Detroit Receiving Hospital No. 235069).—A 49-year-old negro male was admitted with a history of episodic generalized seizures, confusion, disorientation and difficulty in gait. There had been two previous admissions in the past three months which were similar to the admission noted below. He is known to the hospital to be a chronic alcoholic with hepatic cirrhosis. The difficulty in gait began first as a swaying and later he fell frequently, which he attributed to weakness of the legs. This progressed to the point where he was unable to stand without support.

On examination, there was slight scleral icterus and œdema of the ankles. The blood pressure, 172/90, pulse 100 and temperature was normal. There was no cheilosis nor abnormality of the tongue. The heart was enlarged to the anterior axillary line and a grade 3 systolic murmur was present over the præcordium. The liver was enlarged 4 cm. below the right costal margin. The neurological examination showed disorientation to time for he was unable to name the day or the month correctly. He was orientated to place and person but made numerous errors in subtracting 7 serially from 100. There was no confabulation. He showed inability

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to perform abstract thinking and was unable to interpret common proverbs. His gait and station were grossly abnormal but Romberg's sign was not present. He stood with his legs one and a half feet apart, and on attempting to walk, he made ineffectual shuffling movements of the feet. When pushed forward, he made small, staggering steps. When asked why he could not walk he said that he felt nervous because his legs were stiff. He showed slowness and hesitation in performing tests with his feet but was able, after considerable difficulty, to touch the examiner's finger with his toe.

Examination of the cranial nerves revealed no papilloedema and normal pupils. There was no nystagmus, ophthalmoplegia, or signs of Wernicke's encephalopathy. A rapid, fine tremor having 1 cm. excursion was present in both hands and feet. A bilateral grasp reflex was present in the hands but not in the feet, although a tonic flexion response of the toes resulted when the sole of the foot was stimulated in the region of the tarsal arch. Stroking the outer portion of the foot produced an extensor plantar response. The tendon-jerks were symmetrically hyperactive with clonus at the ankles. There was rigidity in passive motion of the legs. Pain, touch, vibration, position sense and two point discrimination were intact.

His course in hospital was complicated by an episode of akinetic mutism (absence of spontaneous movement of extremities, but response on stimulation by moving the limbs and looking at the examiner with the eyes), which persisted for several days and extensive laboratory studies failed to indicate sufficient evidence of hepatic failure to justify a diagnosis of heptic coma. A diagnosis of atherosclerosis with insufficiency of both anterior cerebral arteries was confirmed by carotid arteriography (fig. 5D).

For the sake of brevity only relevant laboratory data will be summarized. Lumbar puncture showed clear fluid without increased pressure, normal protein and no cells. Hæmoglobin, white blood cell count and urine examination were normal. The sedimentation rate was increased to 95 mm./hour. Blood sugar was 95 mg. per cent; blood urea nitrogen 12 mg. per cent. Serum cholesterol was 210 mg. per cent, and serum content of carbon dioxide, sodium potassium and chloride were normal. The serum total protein was 6·7 grammes per cent, globulin 4·5 grammes per cent. Thymal turbidity was 2+, alkaline phosphatase 8·3 Bodansky units, serum bilirubin varied between 3·2 to 4·4 mg. per cent, cephalin flocculation was 4+. Urine porphobilinogen was negative. Electroencephalogram was within normal limits. Chest roentgenogram showed cardiac enlargement. Prothrombin time was 20 seconds (control 14 seconds). Carotid compression test produced syncope after 20 seconds without bradycardia. Left carotid arteriogram showed narrowing of the internal carotid near its division into the anterior and middle cerebral arteries with irregularity and narrowing (stenosis) of the anterior cerebral arteries without displacement (fig. 5).

The patient was treated with low salt diet, digitalis, mercurial diuretics, phenobarbital and dilantin. He gradually became more responsive, aware of his surroundings, and began to walk again with assistance. His apraxia of gait persisted, but he was able to walk short distances unaided. After five weeks he was referred to another hospital for further rehabilitation.

It was concluded that he was suffering from atherosclerosis of the anterior cerebral arteries with episodic circulatory insufficiency of the frontal lobes; the hepatic decompensation may also have contributed to his neurological disability, although this was thought to be of secondary importance.

Case 5 (Detroit Receiving Hospital No. 132685).—This 60-year-old woman entered hospital with the complaint of bloody vaginal discharge. Her past medical and family histories were not relevant to the present discussion. On admission, there were no abnormal neurological findings on examination, but on pelvic examina-

tion, the cervix was closed, displaced to the left and the uterus was enlarged and nodular. Biopsy of the cervix was performed and the uterus sounded after dilatation of the cervix. A nodular and cystic mass was encountered and curettage resulted in an outpouring of necrotic tumour and serosanguinous exudate. On histological section, the material from both cervix and uterus consisted of squamous-cell carcinoma (of the uterus). Roentgenograms of the chest showed multiple nodular densities throughout the lungs due to metastatic disease which showed enlargement on later films. Twelve days after biopsy of the tumour, the patient complained of increasing difficulty in gait and a tendency to fall when walking. On neurological examination, she was orientated and sensible without impairment of memory. Tests of calculation were normal. On tapping the glabella, there was blepharospasm. The cranial nerves were normal and there was no weakness of the limbs. A striking degree of apraxia of the left leg was present. For example, she could not make kicking movements of the left leg although she was able to do so with the right leg. She was unable to walk because the left leg would "stick to the floor" and she could only make shuffling steps with it. There was a sucking reflex and bilateral graps reflexes of the hands and feet. There was rigidity on passive movement of both arms and gegenhalten of both legs. The tendon-jerks were increased in the left arm and leg and the plantar response was extensor on the left. Sensory examination was normal at this time.

One week later, the left leg and arm became weak and there was inattention (extinction) on bilateral stimulation over the left arm and leg when two pin-pricks or light touch stimuli were used. Thereafter there was progressive left hemiplegia.

Bilateral carotid arteriograms were performed three days after the first neurological examination prior to development of hemiplegia. There was displacement of the right anterior cerebral artery to the left due to the presence of a mass in the right frontal lobe.

A diagnosis of inoperable squamous-cell carcinoma of the cervix was made with pulmonary and right frontal cerebral metastases. Three weeks after the onset o neurological symptoms, the patient expired at which time a flaccid left hemiplegia was present. Permission for necropsy was refused.

Laboratory studies were as follows: Hæmoglobin, total white count and differential white count, urine analysis, radioactive iodine uptake over the thyroid gland, rœntgenographic survey of the bones, skull rœntgenogram, blood Kline test and EKG, all within normal limits. EEG showed a basic pattern of activity within the alpha range with well-localized bursts of higher amplitude, slow activity at 4–8 cycles per second, occurring in both frontal regions (fig. 4A). Cerebrospinal fluid was not under increased pressure, the serological test for syphilis and colloidal gold tests were negative. There were no cells and the total protein was 31 mg. per cent.

Case 6 (Detroit Receiving Hospital No. 243009).—A 60-year-old, extremely obese negro (240 lb. weight) was admitted to hospital because of increasing lethargy, hypertension, headache, mental confusion and difficulty in gait. He gave his history in a whisper, stating that he was short of breath. For several months he had noted dyspnœa, orthopnœa and swollen ankles, and was known to have had hypertension for one year. On physical examination, the blood pressure was 250/100, pulse 100, respirations 26 and laboured, with occasional Cheyne-Stokes breathing. The chest was emphysematous with decreased respiratory excursion and there were rales on auscultation of the lung bases. The liver was enlarged 3 cm. below the right costal margin, and there was pitting œdema of the ankles. The heart was enlarged to the anterior axillary line.

On neurological examination, the patient appeared drowsy and lethargic and spoke in a barely audible whisper, his speech being mumbled, dysarthric and thick.

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He showed difficulty in abstract reasoning, but he was oriented to time, place and person. His replies were slow and ponderous and he was unable to interpret proverbs. He was able to subtract 5 and 7 serially from 100 and retain 5 digits forward and repeat 5 backward, but he made errors in simple addition such as 2 plus 5. The pupils were small (2 mm.) but reacted to light. Early papillœdema was present. Examination of the cranial nerves was otherwise unremarkable. Motor strength was normal but he was slow in carrying out motor movements on command. There was a fine tremor of the head, tongue and both hands (5/second, 1 cm. amplitude). There was plastic rigidity in all four extremities on passive movement. He showed apraxia of gait, with difficulty in initiating the first step with either foot, tending to shuffle, to hold the legs apart, and to fall backward. Once he began to walk, however, the gait improved. He had difficulty in turning to either side. When he walked he did not swing his arms but held them flexed across his chest.

Diagnoses of Hypoventilation Syndrome of Extreme Obesity (Berlyne, 1958, also called "Pickwickian Syndrome"), hypertensive cardiovascular disease and insufficiency of both anterior cerebral arteries were made. Lumbar puncture showed an initial pressure equivalent to 600 mm. of water; final pressure 310 mm. after removal of 10 ml. of clear fluid. The cerebrospinal fluid showed no abnormality of protein or cellular content and the Klein test and colloidal gold were negative. The venous pressure was 140 mm. of water and arm to tongue circulation time was 18 seconds. Blood erythrocyte count was 6·41 million, hæmatocrit 50 volumes per cent. Total leucocytes count was 8,000.

Pulmonary function studies performed by Dr. Benjamin Lewis of the Department of Medicine confirmed the diagnosis of pulmonary hypoventilation with oxygen desaturation and CO_2 retention. In the lying position, there was a tidal volume of 423 ml. (the dead air space of the apparatus was 150 ml.) (that of patient was 150 ml.), respiratory rate of 16, oxygen saturation of 79·4 per cent and alveolar pCO_2 of 47·7 mm. of mercury. In the sitting position, the respiratory rate was 27, tidal volume 402 ml., oxygen saturation of 80·2 per cent and pCO_2 of 48 mm. mercury. With oxygen breathing, the oxygen saturation rose to 100 per cent, but the pCO_2 remained 48·3 mm. mercury.

Electroencephalogram showed basic pattern in the alpha range with frequent short bursts of slowing of moderate amplitude in the theta and delta range showing bifrontal preponderance (fig. 4B). Roentgenogram of the chest showed gross generalized cardiac enlargement, with minimal pulmonary congestion. Skull roentgenograms were normal. EKG showed changes due to left ventricular hypertrophy. Radioactive iodine uptake studies showed normal thyroid function. Serum protein, albumen, globulin, glucose, and urea nitrogen content were within normal limits.

The patient was treated with digitalis, weight-reducing diet, amphetamine and diamox. Following six weeks of treatment, he became alert, his gait and neurological examination became normal, the cerebrospinal fluid pressure returned to normal and his pulmonary function studies improved.

Case 7 (Detroit Receiving Hospital No. 260366).—A 59-year-old male machinist was admitted to hospital because of progressive difficulty in walking. He had been known to suffer from hypertension for several years and had suffered a stroke one year before admission with transient weakness of the right side and blindness for several minutes. He was not hospitalized at that time but was treated at home for two weeks by his physician. Since that time, he had noted difficulty in walking, difficulty in bending over and an episodic tendency of the right leg to "drag" when he walked. The past medical and family history were otherwise unremarkable except that ten years previously, he had suffered traumatic amputation of three fingers of the left hand in a punch-press accident and had been troubled by orthopnœa

and exertional dyspnœa for two years. He also complained that when he grasped an object with his right hand, he was unable to let go.

General examination showed the blood pressure to be 180/80, the pulse to be regular (88/minute) and the temperature to be normal. Early cataracts were present in the lenses of both eyes. Although the heart was not enlarged, loud (grade 3) apical and aortic systolic murmurs were present. The first three digits of the left hand were missing and there was pitting œdema of the ankles.

On neurological examination, he was orientated but slow in mentation and speech with labio-lingual (pseudobulbar) dysarthria and immobile facies. He tended to laugh inappropriately. He gave an incorrect interpretation of a common proverb and denied that he had heard of it before. When the glabella was tapped with the finger there was blepharospasm. The fundi were normal save for numerous white perivascular exudates. Examination of cranial nerves was otherwise normal. Examination of the motor system revealed plastic rigidity of the right arm and both legs. A fine, rapid tremor was present in the left arm and leg with bradykinesis of all movements and the finger-to-nose and heel-to-shin tests were performed in a slow, hesitant manner. The gait was slow and shuffling with small steps and difficulty in initiating gait or in lifting the feet from the floor. He could not step out, walk hurriedly or run. There was difficulty in turning to either side and in bending the trunk. His performance in making bicycling movements with the feet in the air was poor, the right leg failing to make circling movements. There was also clumsiness or inability to make circles or write numbers with the feet and toes. He was able to walk crouched on all fours without difficulty but he arose to the standing position slowly. He could turn on to his back or abdomen when in the lying position in a normal manner, but he was unable to tap either heel rapidly on the floor. He was totally unable to hop on one foot and fell when he attempted to do so (fig. 7C). He was able to cross his legs but was unable to kick an imaginary ball (fig. 7D) although he kicked well when a ball was placed before him.

On using the "star-gait" test (Bing, 1956), of having the patient repeatedly move forward and back with his eyes closed, his movements were slow and he steadily deviated to the right (fig. 7E and F). There was no loss of motor strength but when he grasped the examiner's hand with his right hand, there was a delay of 8–12 seconds before he could release his grip ("tonic innervation" of Wilson and Walshe, 1914). Percussion myotonia was not present but a grasp reflex was present in both hands (fig. 7A) and in the right foot (fig. 7B) with a tonic response on plantar stimulation of both feet. The rebound phenomenon of Holmes and Stewart was not present. The tendon jerks were equal but there was clonus in both ankles and the right plantar response was extensor, the left being flexor. Sensory examination was normal in all respects.

Lumbar puncture was performed and showed an initial pressure of 170 mm. and a final pressure of 100 mm. There were no cells but the Pandy test was positive and the total protein was 98 mg. per cent. The Kline test on blood and cerebrospinal fluid was negative. The fasting blood sugar was 107 mg. per cent and the blood urea nitrogen was 18 mg. per cent. Electroencephalogram showed a basic pattern of 10 cycles per second with short bursts of moderate emplitude 4–6 cycles per second slowing occurring bifrontally but with left frontal preponderance. Bilateral carotid and subclavian-vertebral arteriograms showed complete occlusion of the anterior cerebral artery on the left at the origin of the left pericallosal artery. There were also narrowing and sclerotic changes in the right anterior cerebral artery (fig. 6). The origins of both vertebral arteries were narrowed and there was an atheromatous plaque in the left vertebral artery 1½ in. from its origin. There was also elongation, irregular narrowing and reduction in calibre of the basilar artery. The middle and posterior cerebral arteries were normal in position and appearance. He was seen in

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consultation by the Vascular Surgery Service and is returning regularly to the Neurology Clinic. The clinical diagnosis is diffuse cerebral atherosclerosis with occlusion of the left anterior cerebral artery, insufficiency of the right anterior cerebral artery and hypertensive, arteriosclerotic heart disease.

Discussion

In the Introduction, a review of the literature was presented pertaining to disorders of gait that have been described with cerebral lesions. It is apparent that there is disagreement not only concerning the mechanism of the disturbance of gait but also concerning the associated signs of disturbed motor function that are found on examination of such patients. After review of the literature and clinical analysis of our case material, we are convinced that there are three possible mechanisms which may result in disorder of gait and co-ordination as a consequence of cerebral disease. Under the general term of "frontal ataxia" different authors have reported cases of disturbance of gait due to various combinations of three possible mechanisms and we believe this may account for apparent discrepancies in the semeiology of frontal lobe lesions. The three mechanisms by which lesions of the frontal lobe may cause disorders of gait and co-ordination are as follows: (1) Large expanding lesions of the frontal lobe may result in massive displacement of intracranial structures with cerebello-medullary compression resulting in *ataxia* and cerebellar signs (Bruns, 1892; Collier, 1904; Grant, 1928; Frazier, 1936; and Bing, 1956).

(2) Large expanding lesions of the frontal lobe may result in massive displacement of intracranial structures resulting in functional interference of the eighth cranial nerve producing labyrinthine vertigo and *ataxia* (Vincent, 1911).

(3) Localized damage to the frontal lobe without displacement of intracranial structures may give rise to *apraxia* of gait in the absence of damage to the cerebellum (Gerstmann and Schilder, 1926; van Bogaert and Martin, 1929).

In the case material presented here, we have found evidence that the last mechanism, namely apraxia of the legs in walking and co-ordinated movement, does occur and that although it may resemble "*ataxia*" it is truly an *apraxia*, and should be called "apraxia of gait" rather than "frontal ataxia." In this investigation, we have attempted to observe and record data in clinico-physiological terms with a view to finding a suitable definition of "apraxia of gait," to define how the apraxia of the feet interferes with gait and how it may be differentiated during neurological examination from cerebellar ataxia. Ideal cases for such a clinical investigation should not suffer from large expanding lesions of the brain with displacement of brain structures. 6 of the 7 cases described in this report showed no increase in intracranial pressure and in the exception (Case 6) there was no reason to believe that there was displacement of brain. In

5 cases, there was no space-occupying lesion present at all (atherosclerotic stenosis or occlusion of the anterior cerebral arteries in 4 cases, arrested paretic neurosyphilis in 1 case). In the 2 cases of brain tumour, we believe the signs *of themselves* were sufficiently characteristic of apraxia of gait to exclude the possibility of confusion with cerebellar ataxia. Furthermore, the neuroroentgenographic and surgical data excluded the possibility of massive displacement of intracranial structures. For these reasons, the group of 7 cases discussed here provided an unusual opportunity to study the disorder of function resulting in apraxia of gait particularly since the patients were free of aphasia.

Definition of apraxia of gait.—The following definition seems simple and satisfactory: Apraxia of gait due to cerebral lesion is the loss of ability to properly use the lower limbs in the act of walking which cannot be accounted for by demonstrable sensory impairment or motor weakness. This definition is compatible with the views of Wilson (1908) and according to the classification of apraxia described by Liepmann (1914) and Brun (1921, 1922) apraxia of gait would be placed in the limb-kinetic apraxias.

Differential diagnosis between apraxia and cerebellar ataxia.—For comparison with the cinematographic records made in the 3 patients with apraxia of gait, similar records were also made of a young woman suffering from gross cerebellar ataxia. It is our conclusion, in contradistinction to Bruns, that apraxia of gait can readily be recognized from its clinical manifestations and need not be confused with cerebellar ataxia. The principal contrasting features have been tabulated in Table II. In general, features that are characteristic of apraxia of the legs but which are absent in cerebellar disease are slowness in initiation of movement, tendency to deviate to the side of the apraxic limb in performing the "star-gait" test (because the affected limb takes shorter steps and the trunk tends to deviate to the affected side), perseveration of posture, rigidity, gegenhalten, hypokinesis and difficulty in performing such motions with the feet as drawing a circle, tapping the heel on the floor and kicking an imaginary ball.

The nature of apraxia of gait.—The commoner diseases that gave rise to apraxia of gait are tumour, atherosclerosis of the anterior cerebral artery, abscess, paretic neurosyphilis, presenile and senile dementia, and less commonly, cerebral hæmorrhage. However, any disease affecting the mesial aspects of the frontal and parietal lobes may produce this interesting syndrome. Prompted by our interest in this condition, we have recently studied with cinematophotographic records a 31-year-old male with Wilson's disease (associated with Kayser-Fleischer rings, cupruria and hypoceruloplasminæmia), who shows apraxia of gait and movements of the feet (without cerebellar signs) in addition to tonic innervation of the grasp reflex of both hands, grasp reflexes of the feet and generalized rigidity. Although we have not reported any necropsy studies in the 7

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TABLE II.—CLINICAL SIGNS THAT DIFFERENTIATE APRAXIA OF GAIT FROM CEREBELLAR ATAXIA

Clinical sign	*Cerebellar disease*	*Frontal lobe apraxia*
Gait	Faster, feet easily lifted from ground, no shuffling. Irregular placement of feet. "Star-gait" negative. Bilateral instability of legs	Slow, feet rooted to ground, shuffling, short steps, retropulsion common. "Star-gait" usually positive. May be unilateral disturbance
Station	Wide-based, unsteady without movement	Usually wide-based, unsteady with movement
Romberg's test (compare station with eyes open and closed)	Positive in spinocerebellar ataxia; negative in pure cerebellar disease	Negative
Resistance to passive movement	Decreased	Increased, usually rigidity, gegenhalten
Tremor	Slow, coarse, worse terminally	Fine, rapid, appears in action
Dysmetria (past-pointing)	Not improved by volition or repetition. Swaying, rhythmic	Improved by volition and repetition. Not swaying or rhythmic
Perseveration ..	Absent	Present
Tonic innervation ..	Absent	Usually present
Grasp reflex.. ..	Absent	Usually present
Rapid alternating movements	Poorly co-ordinated	Slow, hesitant, or cannot perform
Abstract motions (e.g. kicking imaginary ball, etc.)	Clumsy but rapid performance	Cannot perform or slow performance; difficulty in initiating movement
Holmes-Stewart sign	Present	Absent
Pendulous knee-jerks	Present	Absent
Bilateral simultaneous movements	Same as unilateral	Worse than unilateral
Paucity of spontaneous movement (hypokinesis)	Absent	Usually present
Rising from sitting to standing position	Ataxic but rapid in starting	Slow, hesitant in starting
Walking on all fours	Ataxic	Normal (or slow) without ataxia

cases reported here, one of us (J. S. M.) has examined a patient who presented with unilateral apraxia of gait and later had the opportunity of examining the brain at necropsy. The patient died of pulmonary carcinoma, and in the mesial aspect of the frontal lobe opposite the affected limb, immediately anterior to the precentral gyrus was a small metastatic, round deposit of pulmonary carcinoma measuring $2 \times 5 \times 3$ cm. in

diameter. In this instance, the cerebellum and brain-stem were normal and there was no displacement of brain structure.

The possibility that damage to the fronto-pontile tract may of itself give rise to *cerebellar* symptoms appears to us to be untenable in view of the careful anatomical studies reported by Meyer, Beck and McLardy (1947) in cases of prefrontal leucotomy. In several of the cases reported by these authors there was unilateral or bilateral degeneration of the prefronto-pontile (Arnold's) bundle following lesions in the vicinity of Area 10 and in their clinical case reports there was no mention of ataxia or apraxia of gait. We have also had the opportunity of examining several cases of prefrontal leucotomy in which there was no disorder of gait, although incontinence, inappropriate affect and loss of abstract reasoning were commonly present for a few days immediately following surgical intervention.

The cases reported here confirm the view of Denny-Brown (1958) that release of grasp and sucking reflexes are commonly found in association with apraxia of gait due to presumed lesion of the frontal lobe. A grasp reflex of the feet was not present in all our cases, and unlike the cases reported by Denny-Brown, our patients were unable to move the limbs freely in air (e.g. tapping the heel, making a circle, kicking an imaginary ball). On the contrary, there was evidence of impaired initiation of all movements of the affected foot and leg whether it was on the ground or not, although performance was worse when the feet were on the ground. Futhermore, in several there was a general difficulty in motor performance as exemplified by the apraxia of writing in Case 2 and the slowness, hypokinesis and difficulty in initiation of motor acts present to some degree in all our cases. All our cases did show a "magnetic" attraction of the foot to the ground, but occasionally, the toe was seen to dorsiflex while the foot was on the ground (fig. 1c). It was evident that "tonic innervation," rigidity and perseveration of movement were present in all our cases and interfered with normal motor activity. The grasp reflex when present probably also contributed to this "anarchy" of motor performance. We were of the opinion that the primary difficulty appeared to be in the initiation of a movement, particularly in the abstract performance of motor movement such as taking the first step, in kicking an imaginary ball, in touching an object with the toe, in writing numbers with the feet, in turning, and in some cases, in sitting and standing. The first movements were slowly carried out but once started the performance improved and could often be repeated without difficulty. It appeared to us that in making any motor act on command there was an initial hesitation as though the concept of the movement were intact but its execution was at fault. Since in other respects there was no motor paralysis this can best be explained as a transcortical paralysis. It appears to belong to a type of disorder long recognized in patients with apraxia of the upper limbs

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namely difficulty in making gestures such as waving goodbye, although the same movement can be executed well in less abstract performance such as brushing away a fly. This disorder of abstract motor performance was particularly well illustrated in Case 7. This patient was able to kick a ball placed before him but could not kick an imaginary ball (i.e. make a motion as though kicking a ball). The same kind of difficulty with abstraction was invariably demonstrated in tests of mental function in all our patients (e.g. concrete interpretations were given of commonly used proverbs). This difficulty in abstract reasoning occurring in frontal lobe damage has been emphasized previously by Goldstein (1942). The sign is sufficiently reproducible to be a reliable indication of frontal lobe disease in our hands and appears to be related to the disorder of motor performance of the lower limbs seen in all the patients described here.

Catonia is relatively rare as a manifestation of cerebral disease but was well exemplified by Case 2 (fig. 3A). Catatonia appears to be a part of a severe apraxia and in cases with frontal lobe damage is closely related to perseveration of posture and tonic innervation. Hypokinesis and bradykinesis appear to be less severe degrees of catatonia. The catatonia seen in frontal lobe disease is similar to that seen in parietal lobe disease, but in the latter, the immobility appears to be a simple unawareness of the limb due to a perceptual disorder.

Analysis of this series of cases leads us to the conclusion that apraxia of gait is due to a disturbance of initiation of movement at a cortical level; it is a transcortical innervatory paralysis. It can be shown in all our patients that the motor mechanism for movement of the legs remained intact, cerebellar signs were absent and the cortical spinal tracts showed little or no damage. Motor strength was intact but the motor mechanism was not available except for the simplest of movements. The concept of movement was at least partially intact but resulted in an insecure and hesitant response which was further interfered with by tonic innervation and gegenhalten. The latter signs are further evidence of release from cortical control (in the sense of Hughlings Jackson) for it is generally agreed that they are seen only following frontal cortical lesion.

It was evident in cases with unilateral involvement (Case 5) that the motor performance of the affected limb was rendered worse when bilateral movement of both limbs was attempted. In the other cases with bilateral involvement, movement of either limb alone was better than when both limbs were moved together. This disintegration of performance when both limbs are used together is seen following corticospinal tract injury (Hausmanowa-Petrusewicz) and parietal lobe injury (Denny-Brown, Meyer and Horenstein, 1952). It appears that the performance of one damaged hemisphere essentially functioning on its own in the simple use of the opposite limb deteriorates when the other hemisphere (and limbs) are called upon to function simultaneously.

Apraxia of gait thus appears to be due to a trans-cortical innervatory paralysis of the lower limbs made worse by tonic innervation of the feet, rigidity and gegenhalten. Attempts at walking are further hindered by the simultaneous movements of both legs necessary in the act of walking, since bilateral, simultaneous motor movement further compromises an insecure cortical innervation of unilateral movement.

SUMMARY

Review of the literature pertaining to disturbance of gait associated with lesions of the cerebrum shows that there is general disagreement concerning how this symptom is produced. In large space occupying lesions of the frontal lobes with brain displacement, the cerebellum and medulla may be compressed, giving rise to true cerebellar signs, or the eighth cranial nerve may be stretched, causing vertigo and ataxia. In cerebral lesions, without displacement of brain, such as infarction of the frontal lobes due to atherosclerosis of the anterior cerebral arteries, apraxia of gait may result. Apraxia of gait is defined as the loss of ability to use the lower limbs in the act of walking which cannot be accounted for on the basis of demonstrable sensory impairment or motor weakness. Clinical investigation of 7 cases with apraxia of gait is reported here and signs that may be used to differentiate *apraxia* of the legs from cerebellar *ataxia* are described. It may be shown by standard tests in cases of apraxia of gait that there is apraxia in all movements of the lower limbs together with motor signs of release from cortical control such as rigidity, tonic innervation and gegenhalten. Signs of difficulty in abstract reasoning are usually present and abstract movements of the feet (e.g. kicking an imaginary ball or making a circle with the feet) are impossible or severely impaired. Difficulty in initiating all movements of the feet is present. Unilateral movements of the foot are performed better than bilateral simultaneous movements of the feet. It is concluded that apraxia of gait results from a transcortical innervatory paralysis of the legs, worsened by tonic innervation, rigidity and gegenhalten. In addition, gait is worsened by the fact that bilateral simultaneous movement of the legs is essential to walking.

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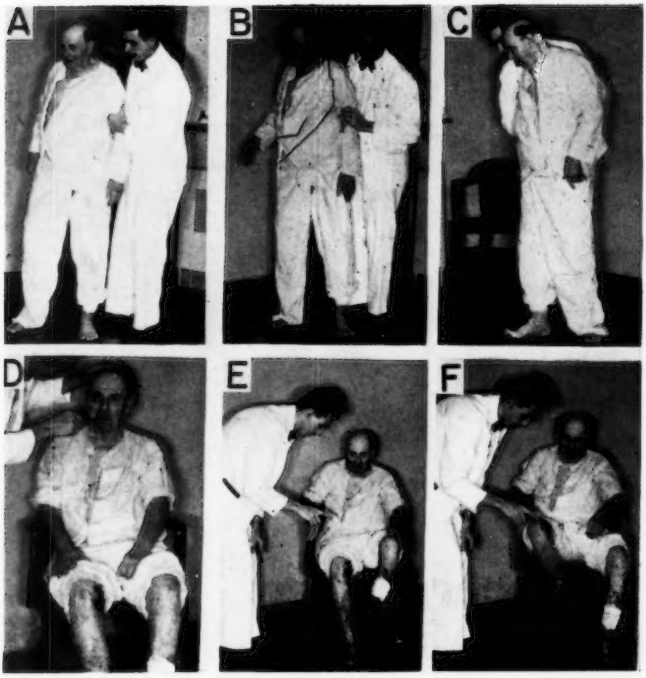

FIG. 1.—Single frames from a moving picture of Case 1. A, Patient attempting to walk, difficulty in initiating first step with right leg. B, Similar difficulty in making first step with left leg. C, To show difficulty in turning, note extension of toe. D, To show sucking reflex. E, Attempting to touch examiner's finger with left leg (apraxia). F, Apraxia of right leg in attempting to touch examiner's finger.

To illustrate article by John S. Meyer and David W. Barron.

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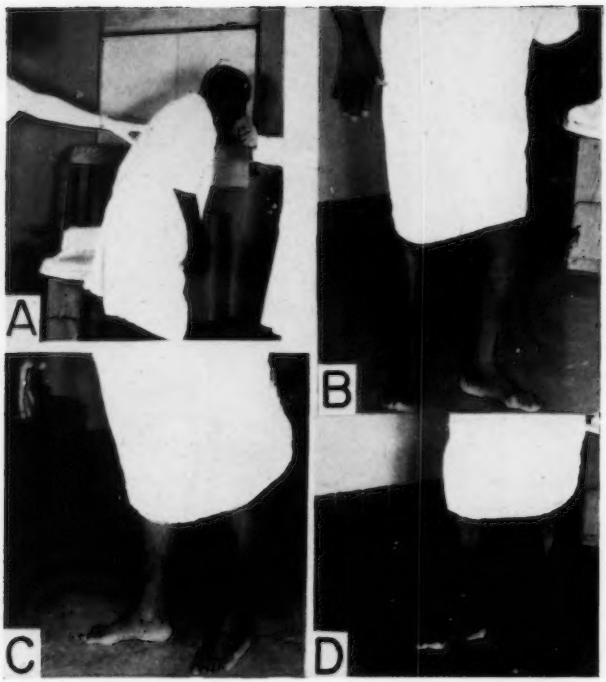

FIG. 2.—Single frames from a moving picture of Case 2. A, Patient unable to initiate gait even when propelled by staff-physician. B, Attempting to step out and walk with left foot, note balancing movements of hands. C, Similar disorder on attempting to step out with right foot. D, After many efforts, the right foot is finally raised a few inches and shuffling step is made.

To illustrate article by John S. Meyer and David W. Barron.

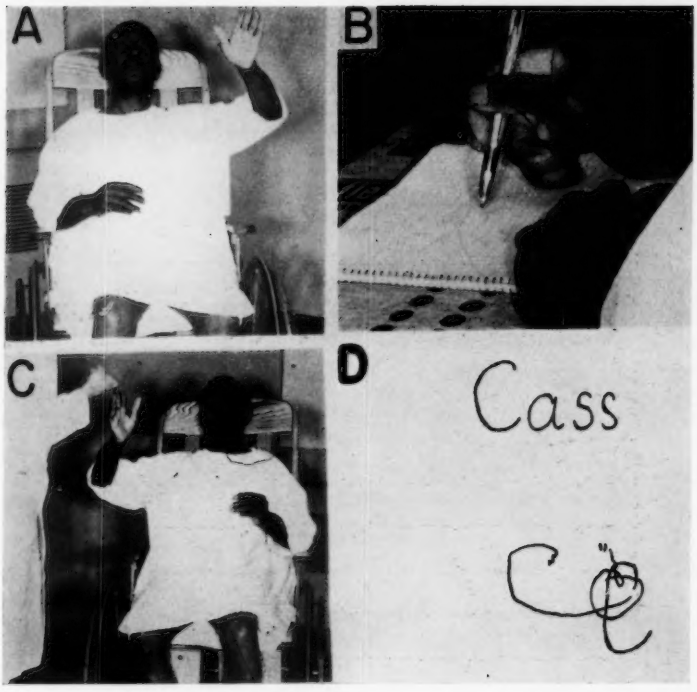

FIG. 3 (*Case* 3).—A, To show catatonic posturing due to perseveration of posture. B, Motor apraxia of writing, note pen held stiffly, and too high. C, Apraxia, with perseveration of posture on finger to nose test (*see* text). D, Attempts to copy his first name, perseverates with first letter. Note hesitant "scratch" marks at beginning of first "C".

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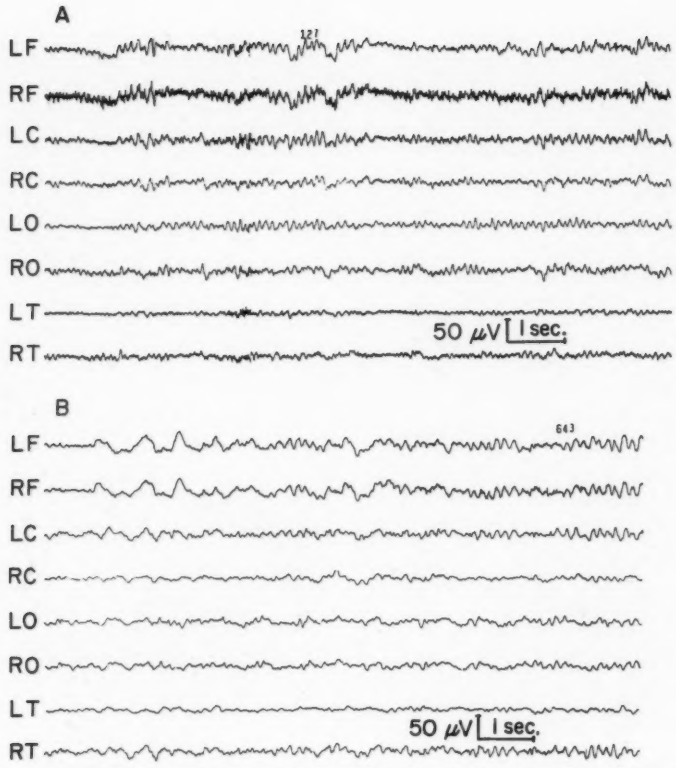

FIG. 4.—A, Electroencephalographic record of Case 5 (metastatic carcinoma of frontal lobe) made in the alert state without hyperventilation. There are bilateral bursts of slow activity in both frontal regions. B, Electroencephalographic record from Case 6 (anterior cerebral artery insufficiency, hypoventilation syndrome) at the time apraxia of gait was present. There is preponderance of slowing in both frontal regions. After weight reduction, his record improved and became normal.

To illustrate article by John S. Meyer and David W. Barron.

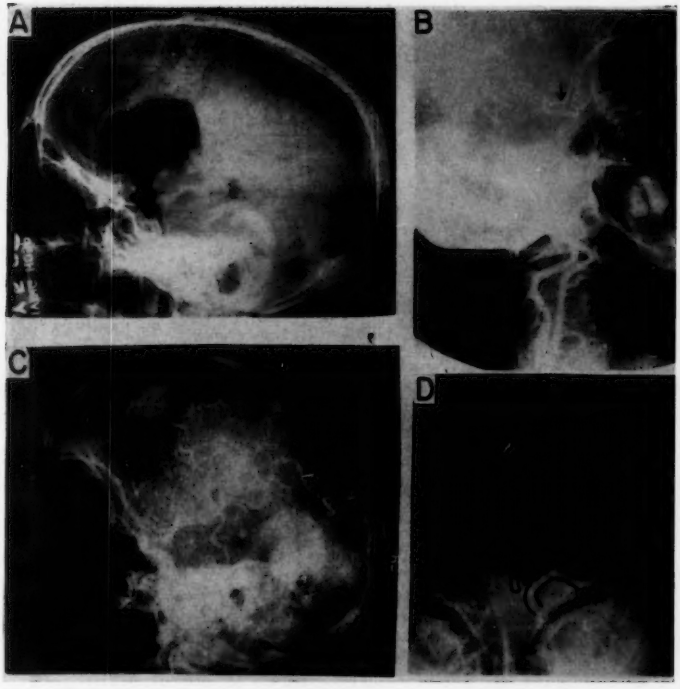

FIG. 5.—Roentgenographic studies of Cases 1–4. A, Pneumoencephalogram showing dilatation of both frontal horns in Case 2. B, Case 1, carotid arteriogram. The arrow points to narrowing of the proximal portion of the anterior cerebral artery. The middle cerebral artery is also stenotic. C, Case 3, right carotid angiogram showing displacement of pericallosal and callosomarginal arteries around a right frontal parasagittal mengioma. D, Case 4. Arteriogram showing atherosclerotic stenosis of right anterior cerebral artery (vessel shadow outlined with india-ink).

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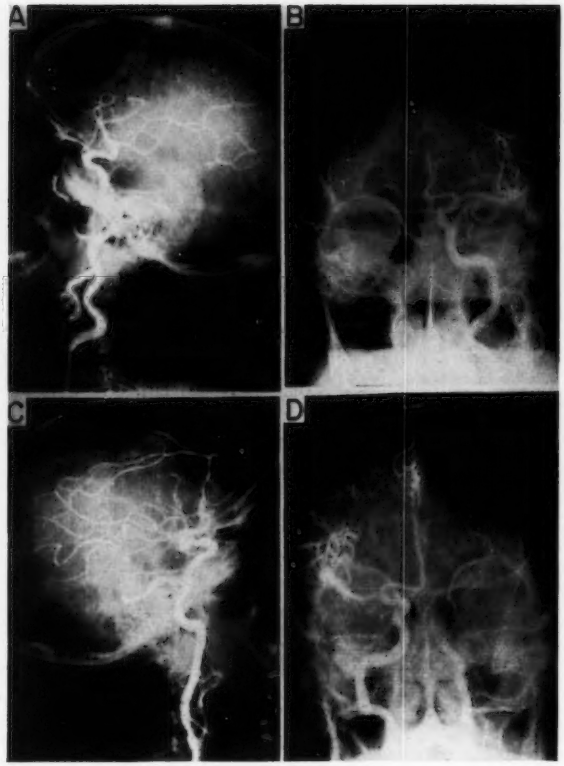

FIG. 6.—Carotid arteriograms in Case 7. A, To show occlusion of pericallosal branch of left anterior cerebral artery, lateral view. B, Anterior-posterior view. C, To show stenosis of right anterior cerebral artery (lateral view). D, Anterior-posterior view.

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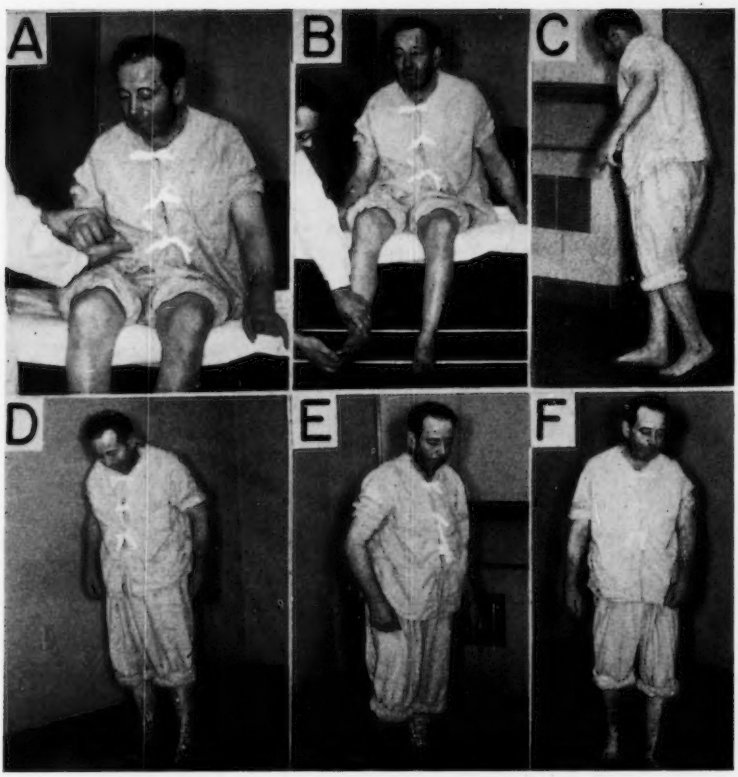

FIG. 7.—Single frames from a moving picture of Case 7. A, To show tonic grasp reflex ("tonic innervation") of right hand. B, To show grasp reflex right foot. C, To demonstrate inability to hop on one foot. E, To show the phenomenon of "star-gait." Here he is moving forward for the first time with eyes closed. F, After repeating this manœuvre eight times he is facing 45 degrees to the right.

To illustrate article by John S. Meyer and David W. Barron.

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INTRASPINAL TUBERCULOUS GRANULOMA

BY

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INTRASPINAL tuberculous lesions have been known for a long time, the first description of a tuberculoma of the spinal cord was given by E. R. A. Sérre in 1830 (according to Thalhimer and Hassin, 1922; in Kupka and Olsen, 1938), while the first removal seems to have been performed by Krauss and McGuire in 1909. Their frequency is very low if extradural tuberculous lesions associated with Pott's disease are ruled out. This accounts for the fact that though 171 cases were reported in the literature until 1956 (Dibble and Cascino, 1956) (many of them being, in fact, necroptic findings), the contributions of all authors are based on one or very few personal patients (Weinberg, 1926; Kupka and Olsen, 1938; Arendt, 1951; Dibble and Cascino, 1956; Bertrand and associates, 1958; Thurel, 1958).

We hope therefore that a presentation of the authors' personal experience in the treatment of a somewhat larger series of patients may prove useful.

Incidence Rate, Age, Sex

According to Bucy and Oberhill (1950), in 6,000 post-mortem examinations Wilson, Rupp and Bartle (1941) found 6 intraspinal tuberculomata (3 of these cases had tuberculomata also in other portion of the central nervous system). In the literature up to 1935, Kupka and Olsen (1938) found 87 cases of tuberculoma of spinal cord, while Dibble and Cascino (1956) found 48 more cases published in the literature during the 1935–1956 period.

In the "Prof. D. Bagdasar" Neurosurgical Clinic, Bucharest, we found 9 intraspinal tuberculous granulomata in a series of 38,510 patients seen between 1935 and December 31, 1957. During the same period we encountered 201 intracranial tuberculomata (Arseni, 1958) and 430 intraspinal tumours of different natures (Arseni and Ionesco, 1958). This amounts to an approximative proportion of 1/20 between intraspinal

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and intracranial tuberculous granulomata, and to an approximative proportion of 1/43 between tuberculous and non-tuberculous expanding intraspinal lesions.

Most of the patients with intraspinal tuberculous granulomata were in the younger age-groups: the average age was 23 years 5 months; 7 out of 9 patients (78 per cent) were younger than 30 years, and the 2 older patients were 48 and 41 years old respectively. As regards sex, males are more frequent in our series.

Pathology

There is unanimous agreement on the fact that intraspinal tuberculous lesions are secondary tuberculous lesions, yet in 3 patients we are unable to detect any other tuberculous lesion, either in the past history or at the time they were admitted to hospital; on the other hand, the past history disclosed pulmonary tuberculosis in 3 patients and tuberculous meningitis in 2 patients, while 2 patients displayed extrapulmonary forms of tuberculosis at the time of admittance to hospital (tuberculosis of the hip and orchiepididymitis respectively). The latter case is among those which displayed pulmonary tuberculosis in their past history.

It must be noted that in 1 of the 3 patients in whom no other tuberculous lesion could be found either in the past history or upon admittance, necroptic examination performed in another clinic eight months after operation revealed multiple tuberculomata of the brain which caused the death. None of the patients except the latter one could be proved to have a co-existing tuberculoma of the brain (with clinical symptoms), nor did any of the 201 patients with cerebral tuberculomata (Arseni, 1958) display a simultaneous intraspinal tuberculoma as was stated through inadvertence by Martin (1958) in reference to another paper by one of the authors (Arseni, 1957).

The gross, and especially the microscopic features of tuberculomata of the spinal cord have been very accurately depicted by Hassin (1933).

Extradural tuberculomata are often ring-shaped, forming a more or less complete cover around the dura mater; their size is 3–5 mm. thick and 5–7 mm. wide; it adheres to the dural membrane, from which it can nevertheless be detached. It has a lardaceous, non-hæmorrhagic appearance and may be mistaken for a meningioma or chronic epiduritis.

Subdural tuberculomata are hard, round or oval-shaped; their size ranges between that of a cherry-stone and a plum-stone. It is usually attached by close adhesions to the inner aspect of the dura mater and to the spinal cord into which it digs a crater, so that it is occasionally difficult to say whether a subdural tuberculoma is extramedullary, or intramedullary emerging to the surface after having broken through the spinal cord. In point of fact, after revising the operation records and the subsequent evolution of the patients the authors reached the conclusion

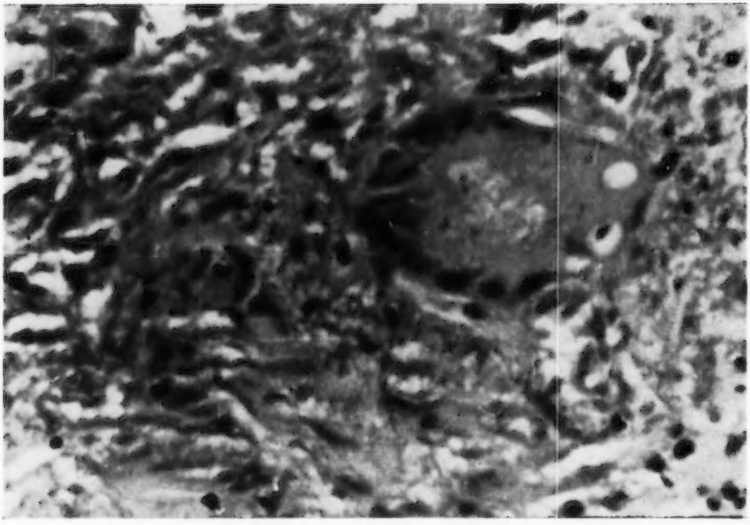

FIG. 1.—Giant Langhans cell in a tuberculous folliculum. Near-by a zone of necrosis is seen as well as a zone of lympho-plasmocytic infiltration of low density. H.E. × 950.

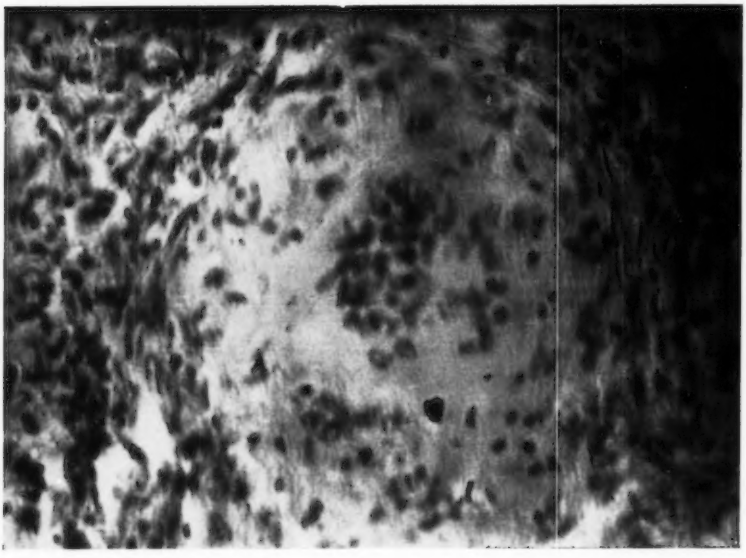

FIG. 2.—A giant Langhans cell in the process of formation. Marked necrosis around it. At the periphery of the image relative dense small round cell infiltration. H.E. × 650.

To illustrate article by Constantin Arseni and Dinu C-Tin Samitca.

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that 2 of the cases considered in another paper (Arseni, 1957) as intramedullary tuberculomata emerging through the spinal cord were actually extramedullary subdural tuberculomata which had made a crater into the spinal cord.

Intramedullary tuberculomata determine a deformity of the respective portion of the spinal cord, they are hard and circumscribed, measuring 7–10 mm. in diameter. They are often associated with a more or less intense local arachnoiditis. As a rule intramedullary tuberculomata can be easily enucleated without any excessive trauma to the spinal cord.

Intramedullary tuberculomata have a whitish appearance. In their central portion, however, they may contain a caseous area or sometimes a gelatinous translucent greenish area with an irregular outline. Their periphery is formed of a hard fibrous area. Microscopic examination of an intraspinal tuberculoma reveals a central area of necrosis while the periphery is formed of granulation tissue which often contains Langhans giant cells and epithelioid cells (figs. 1 and 2, Plate XL).

Of the 9 intraspinal tuberculous granulomata encountered in our Clinic, 1 was extradural, 3 were subdural extramedullary and 5 were subdural intramedullary. The extradural tuberculoma has been included in this series, because it was not a case of tuberculous epiduritis associated with Pott's disease, as was proved both by roentgenologic examination and by the operative findings.

As regards the site of the intraspinal tuberculous granulomata in this series, most of them (6) were thoracic while 1 was cervical and 2 were lumbar; this differs from the literature data assembled by Kupka and Olsen (1938), according to which they are almost equally distributed between the cervical, thoracic and lumbar regions of the spine.

Clinical appearance

As the spinal cord is extremely sensitive to compression, the clinical evolution is usually a rapid one; in our patients its duration ranges from one and a half to eight months with an average of three and a quarter months.

In all the 8 cases of subdural intraspinal tuberculous granulomata, irrespective of their extra- or intramedullary origin and of the level of the lesion, the clinical picture rested on a symptomatic tripod formed of motor, sensitive and sphincteric disturbances. Thus in 5 cases the patients had paraplegia (flaccid in 2 cases and spasmodic in 3 cases); 1 case had spasmodic tetraplegia while in 2 cases there was spasmodic paraparesis. Hypoæsthesia or anæsthesia whose upper limit was corresponding to the site of the lesion was present in all cases, while 7 patients had sphincteric disorders (Table I).

Pain was never present throughout the course of these cases of subdural tuberculous granulomata (8); it must also be pointed out that none of

TABLE I

Anal sphincter	*Vesical sphincter*	*No. of cases*
I	I	2
R	R	2
R	I	1
N	I	1
N	R	1

I = incontinence. R = retention.
N = normal.

the cases displayed a Brown-Séquard syndrome, though one of the patients seem to have had a Brown-Séquard syndrome at a certain time in the course of his disease (*see* case-record of patient C. M.). In the case of extradural intraspinal tuberculous granuloma the above mentioned tripod was absent as the patient only complained of bilateral lumbosciatic pain and had Lasègue's sign present on both sides (in this case the site of the lesion was identified by means of a lipiodol myelography).

Paraclinical examinations.—Radiographs of the spine were normal in all cases. A lipiodol myelography was performed in 7 cases and was found to be normal in a single case; in the remaining cases it revealed a total block 4 times and an impaired passage in 2 cases. In most of the cases cerebrospinal fluid examinations revealed xanthochromia and an increased amount of albumin while in 3 cases there was a moderate decrease of chlorides. Other laboratory examinations were within normal limits with the sole exception of the E.S.R. which was sometimes considerably increased.

Case Abstracts

We will now present the case-records of 3 patients: 1 had an extradural intraspinal tuberculous granuloma, another one had an extramedullary subdural granuloma and the third had an intramedullary tuberculous granuloma.

Intraspinal Extradural Tuberculous Granuloma

Case 3.—I. P. (case-record 9010), a 26-year-old male was admitted to the "Prof. D. Bagdasar" Neurosurgical Clinic on March 21, 1950, complaining of lumbosacral pain irradiating into the lower limbs, predominantly in the left one. The family history revealed no significant facts; the patient had had right pleurisy in 1948.

Three months before admittance, one week after he had lifted a heavy weight, he developed pain in the lumbosacral area irradiating into the left lower limb associated with paræsthesia in that limb. The pain grew progressively more intense and it extended into the right lower limb as well. During the last six weeks before the patient's admittance, the pain became so intense that he was unable to walk which determined him to seek hospital treatment. Upon admittance visceral examination was negative, the patient had a good general condition and no fever.

Neurologic examination revealed very intense pain in the lumbosacral region

irradiating into both lower limbs associated with paræsthesia. The pain was aggravated by coughing. Percussion of the second and third lumbar spinous processes determined local pain. Lasègue's sign was present on both sides. There were no other neurological signs or symptoms.

Paraclinical examinations.—The blood count was normal. A simple radiograph of the vertebral column was normal. Lipiodol myelography revealed a total stop of the lipiodol at the level of the 2nd lumbar vertebra.

A tentative diagnosis of radicular compression of undetermined origin was made and the patient was operated upon on March 27, 1950, under spinal anæsthesia with 1·3 c.c. of percaine 0·5 per cent. A left L_2-L_3 hemilaminectomy revealed a hard mass situated dorsomedian at the level of L_2. The hemilaminectomy was widened into a complete L_2-L_3 laminectomy and the mass was seen to adhere to the yellow ligament. By blunt dissection the mass was removed; on its lateral aspect it was bordered by granulation tissue which was likewise removed. The dura mater was not opened. Suture in 4 layers. The removed growth was nearly as big as a cherry and its central portion was caseous. Anatomopathologic examination identified it as a tuberculoma. The post-operative course was uneventful though no streptomycin was administered and the patient was dismissed from the Clinic on April 14, 1950.

Re-examined two years later, the patient had no complaint excepting mild and intermittent lumbar discomfort.

Intraspinal Subdural Tuberculous Granuloma

Case 7.—C. M., a 20-year-old female (case-record 20,583) was admitted to the "Prof. D. Bagdasar" Neurosurgical Clinic on December 21, 1954, complaining of motor weakness and a sensation of numbness in both lower limbs as well as of sphincteric disturbances. The family history revealed nothing of importance. In the patient's past history we noted a tuberculous meningitis which had set in six months before.

The tuberculous meningitis was diagnosed in July 1954 and a treatment consisting of streptomycin administered intramuscularly and intrathecally was started. In August the patient developed intermittent incontinence of urine and in October she noticed the onset of progressive motor weakness in the right lower limb. In December she began to feel a numbness in the left lower limb. Soon afterwards both the motor weakness and the numbness became bilateral whereupon the patient was referred to the Neurosurgical Clinic. Upon admittance the patient's condition was good; she had no fever and visceral examination disclosed nothing of importance.

Neurologic examination disclosed a marked decrease of the muscular force in both lower limbs predominantly on the right side, very increased myotatic reflexes in the lower limbs and the presence of Babinski's sign on both sides. The presence was noted of thermo-algesic anæsthesia with an upper limit at D_7 as well as of intermittent vesical incontinence.

Paraclinical examinations revealed an E.S.R. of 5–8 mm., hypochromic anæmia and an eosinophilia (10 per cent eosinophils). Queckenstedt-Stookey's test showed a blockage of the subarachnoid space. C.S.F. examination was normal. Lipiodol myelography revealed an impaired passage of lipiodol between Th_1 and Th_8.

A tentative diagnosis of compression of the spinal cord in the thoracic region probably due to a tuberculous granuloma was made and the patient was operated upon on January 4, 1955, under local anæsthesia with novocain 1 per cent. A D_6–D_{10} laminectomy was performed. When the dura mater was opened an intense process of arachnoiditis was found. At the lower end of the incision the presence of a hard uneven yellowish structure which compressed the cord was noticed; its site was medial towards the right side. After division of the arachnoid adhesions the mass

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was partly removed by blunt dissection. The wound was sutured in 4 layers. Anatomopathologic examination identified the process as a tuberculoma. After operation the patient was given 70 grammes streptomycin (1 gramme daily by *intramuscular route only*), and 500 tablets of isoniazid. Upon leaving hospital on March 14, 1955, the patient displayed only a slight spasmodic paraparesis; the disturbance of sensibility and the sphincteric disturances had subsided.

Intraspinal Intramedullary Tuberculous Granuloma

Case 8.—I. T. a 25-year-old male (case-record 31.858) was admitted to the "Prof. D. Bagdasar" Neurosurgical Clinic on April 12, 1956, complaining of motor weakness in both lower limbs, disturbances of sensibility in both lower limbs and sphincteric disturbances.

The family history revealed nothing of importance. In the past history of the patient we noted a pleurisy in 1951 and a left chronic orchi-epididymitis (tuberculous ?) detected two months before his admittance to the clinic.

One month before admittance to the clinic the patient noticed the onset of a feeling of numbness in both lower limbs and paræsthesia with the same localization. Shortly afterwards he developed progressive muscular weakness in both lower limbs which resulted in complete paraplegia within two weeks. Urine retention set in one week before admittance.

Upon admittance the patient's general condition was good and he had no fever.

Visceral examination revealed the signs of a left chronic orchiepididymitis. Neurological examination disclosed the presence of a complete paraplegia. The patellar reflexes were markedly diminished and the achillean ones were very lively. Plantar clonus was present on the left side. Thermo-algesic anæsthesia was present with an upper level at T_6, the area between T_6 and T_4 being hypoæsthesic. Urine retention.

Paraclinical examination revealed an E.S.R. of 50–94 mm. and a hypochromic anæmia. A simple radiography of the thoracic spine was normal Lipiodol myelography showed a mild impairment of the lipiodol passage in the upper thoracic region though there was no conclusive appearance. Examination of the C.S.F. was normal.

A tentative diagnosis of compression of the spinal cord in the thoracic region probably due to a tuberculous granuloma was made and on April 13, 1956, a Th_2–Th_4 laminectomy was performed under local anæsthesia with novocain 1 per cent. When the dura mater was opened, at the level of Th_3 the spinal cord was enlarged and hard. Because of the dense vascularity the spinal cord could not be incised on the mid-line; a right lateral incision was made and a hard round-shaped mass the size of a pea was curetted out of the cord. The bleeding was minimal. The dura mater was closed and the wound sutured in 4 layers. Anatomopathologic examination identified the specimen as a tuberculoma. The patient had an uneventful post-operative recovery. The post-operative treatment consisted of 115 grammes streptomycin (1 gramme daily *given solely by the intramuscular route*) and 1,000 tablets of Isoniazid. Upon leaving hospital the patient no longer had any disturbances of sensibility or sphinctera. He only had a mild spasmodic paraparesis.

Treatment

8 out of the 9 patients in our series sustained an operation; the non-operated one developed during his stay in hospital a tuberculous meningitis which was the cause of this death. In this case post-mortem examination revealed an intramedullary tuberculous granuloma. In all

8 cases in which an operation was performed the procedure consisted of laminectomy at the respective level and removal of the lesion, usually under local anæsthesia. This was possible even in cases of intramedullary granuloma for as has been pointed out in relation to the anatomo-pathologic features, the intramedullary tuberculous granuloma is small, hard, and sharply delimited, hence apt to be removed.

As regards the post-operative treatment with tuberculostatic agents (streptomycin, Isoniazid, PAS) it was applied in 6 cases; the amount of streptomycin ranged from 23 grams (certainly insufficient, but the patient in question could not be given a complete treatment as his family objected to his continuing to stay in hospital) and 150 grams streptomycin in *exclusively intramuscular administration* at the rate of 1 gram daily. Streptomycin was occasionally associated with Isoniazid at the rate of 10 mg./kg. body weight daily and perfusions of 3 per cent PAS in a daily amount of 250 c.c.

Of the 2 patients who underwent no antibiotic treatment after operation, one was the case of an intraspinal extradural tuberculous granuloma and one had an intramedullary tuberculoma. The fact that the former patient developed no complication is not very surprising, but we were indeed astonished at the latter patient not developing tuberculous meningitis, though as mentioned in the literature (Veraguth and Bruns, 1910; Elsberg, 1917) intramedullary intraspinal tuberculous granulomata are known to be sometimes successfully removed without antibiotic cover.

Results

As has been pointed out, one of the patients was not operated upon and died of tuberculous meningitis during his stay in hospital. 8 patients were operated upon with no operative mortality. One patient only can be considered as cured (restitutio ad integrum), namely the one with an intraspinal extradural tuberculous granuloma. He was last re-examined two years and two months after operation. Of the 7 patients harbouring intraspinal subdural extra- and intramedullary tuberculous granulomata, 4 showed a marked improvement, the neurological picture remained unchanged in 2 cases and one case was aggravated. It must be pointed out that among the 4 patients operated with intramedullary tuberculomata only 1 was markedly improved upon leaving hospital. 1 of the patients with an intramedullary tuberculoma was unimproved upon leaving hospital, died eight months later in another neurological clinic (after he had somewhat improved) with symptoms of intracranial tuberculomata. None of our patients developed tuberculous meningitis after operation.

Conclusions

Intraspinal tuberculous granulomata are an extremely infrequent condition. They occur almost exclusively in patients aged below 30 years.

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In most of the cases they are intramedullary, which accounts for the rapid clinical course, the severe neurological picture and the unsatisfactory operative results. A correct preoperative diagnosis is only possible when a young patient having a tuberculous lesion elsewhere develops a severe picture of spinal cord compression with a rapidly advancing course. If tuberculous meningitis has been present in the past history, the differential diagnosis should be made with tuberculous arachnoiditis. Otherwise the differential diagnosis is made with all the lesions that may determine a picture of spinal cord compression.

Though it is technically possible to remove even intramedullary tuberculous granulomata and tuberculous meningitis is no longer to be feared as an operative complication owing to the use of tuberculostatic therapy, surgical results are disappointing; this does not apply to extradural intraspinal tuberculous granulomata, nor to subdural extramedullary ones.

As it is difficult, if not impossible, to differentiate extra- and intramedullary intraspinal tuberculous granulomata before operation as both types determine almost the same clinical and radiologic picture, surgery must be undertaken in all cases in order not to deprive patients with an extramedullary tuberculous granuloma of the chance of an improvement which is very often quite remarkable.

Summary

The authors report on 9 personal cases of intrarachidian tuberculous granuloma. Their pathology and clinical aspects are discussed and the results of treatment are reported.

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STUDIES ON CEREBRAL BLOOD FLOW IN MAN, USING RADIOACTIVE-LABELLED ERYTHROCYTES

BY

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AFTER a long search for an indicator which, in contrast to indicators previously used, would not be soluble in water or in plasma and would not penetrate the capillary wall, Nylin (1942, 1943) began to use radioactive-labelled erythrocytes. The basis of the method is that some cubic centimetres of the patient's own blood are labelled and then injected into the arterial or venous system with the purpose to study above all the mixing conditions of the indicator with the blood in the body. The method has been used for circulatory studies of several kinds, Nylin, Hevesy, Hedlund and co-workers (1945, 1953, 1955, 1957, 1958).

Recently this method was tried in studies of blood circulation in the brain. Five years ago Nylin, Blömer (1955) and co-workers (1956) started attempts on a modest scale to inject the labelled erythrocytes into a carotid artery and afterwards collect the blood from the jugular bulb.

One of the purposes of the present investigation was to study the cerebral circulation in cerebrovascular diseases. The cerebral circulation has earlier been the subject of extensive investigations with the Kety-method (1948, 1953). This method has given information concerning the blood flow of the brain in normal and pathological cases (Kety, Bernsmeier). In atherosclerosis, however, surprisingly small changes of the blood flow were found as stated by Lassen (1959). "The measurement of total cerebral perfusion or the cerebral venous oxygen tension cannot, in the average case, disclose the presence of atheromatosis of the cerebral arteries, not even when studies are made during induced hypotension or carbon dioxide inhalation."

The labelled erythrocytes showed distinct advantages to other indicators such as dyes and a little more than a year ago we were able to embark on a rather comprehensive team-work project.

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METHODS

The Labelling and Sampling Technique and Measuring of Radioactivity

The injection of a few cubic centimetres of the patient's own labelled blood is, of course, essentially physiological, and the radioactivity is negligible. The object is to inject the labelled blood into the carotid artery and later, when it has passed through the circulatory system of the brain, to sample it at the main outflows from the brain, viz. the jugular bulbs, and finally to prepare and measure the radioactivity of the samples in the laboratory.

(1) *Labelling technique.*—During the course of the years, Nylin, together with de Hevesy and S. Hedlund, has tried various radioactive substances, such as P^{32}, K^{42}, Thorium B and Cr^{51}. Which labelling substance is to be preferred depends on the circulation problem that it is desired to study. When it is a question of experiments of short duration, P^{32} has proved superior. The labelling is done by taking a blood sample from the patient and shaking it with radioactive phosphate (approx. 7/100 mC per 10 c.c. of blood) in a water-bath at body temperature for a certain time (one hour). The radioactive phosphate penetrates the erythrocytes and is retained within these for quite a long period without in any way damaging them. We separate the labelled erythrocytes from the active plasma by centrifuging and then wash twice with physiological saline in order to free the erythrocytes from adherent activity from the plasma. Then, to the labelled and washed erythrocytes we add unlabelled plasma from the patient in hæmatocrit proportion. The blood sample is now ready for injection into the patient. The quantity of blood which is injected is exactly 3 c.c.

(2) *Sampling of blood.*—The technique of taking the samples from the jugular bulbs is very important. Therefore, with the help of one of the chief designers of the LKB, we have constructed a special sample-collector. With this apparatus it is possible to collect blood simultaneously, once a second, from three places in the circulatory system. The collection from the places of puncture is done in small glass tubes which are moved automatically under the ends of the catheters (figs. 1 and 2, Plate XLI).

After the labelled erythrocytes have passed through the brain, the collected blood samples are prepared according to a special procedure which has been developed in our laboratory. The samples are pipetted in a fixed quantity into small metal bowls, the bottoms of which are covered by a layer of chromatography paper of known quality and dryness. The pipetted samples, which sometimes have to be weighed, are then dried at a temperature of 90° C. for one hour.

(3) *Measurement of activity.*—After drying, the blood samples are ready for measurement of activity. They are stapled in cassettes and put in the so-called robot scaler, a device, specially designed by LKB,

and which is capable of measuring more than 400 samples. The samples are automatically introduced and changed under the G.M. tube. A computer automatically gives the number of impulses as well as the time during which the measuring has been in progress and also records the number of each sample. The apparatus operates day and night without attention. And without it we should not be able to carry out the kind of investigations which will now be described (fig. 3, Plate XLII).

The labelling method, developed and used in our laboratory, shows a very small error. We have calculated the error in the method from the moment we sampled the blood from the patient, during the pipetting or weighing of the sample, the drying and the measuring in the robot scaler, and this experimental error is only 1·5 per cent.

Some of the most intractable sources of error have been as follows:

(1) When trying to determine the cerebral blood flow, it is of great importance that the needle for injection should be in the internal carotid artery and that the labelled erythrocytes should not regurgitate to any noteworthy degree but should really enter the brain. It is only of minor importance for the determination of the circulation times and for analysing the type of the curves whether the needle is in the internal or the common carotid artery. In all cases the position of the needle and the possibility of regurgitation into the external carotid has been checked by X-ray picture of the region in question during injection of contrast medium.

(2) We have catheters of a definite length and diameter for the sample collector. The question has arisen whether a laminar flow can occur here which would upset our results. We have therefore filled catheters with small glass pellets to examine for turbulence and we have been unable to find any perceptible differences between these types of catheters. We have also taken dilution curves simultaneously through two catheters, one 10 cm. long and the other the length we use (50 cm.) and no difference was found. In practice—and empirical experience is not to be despised—it has proved that our curves are highly reproducible, as is shown by the following illustration (fig. 4). This represents 2 bulb curves from the same bulb after double injection in the same artery. We have a whole series of such curves. Corrections for the elapse of time through the catheters are made.

(3) Temporary changes of cerebral blood flow mainly through a fall in the blood pressure, which could vary our results, are not to be disregarded. Blood pressure and pulse have therefore been followed during the investigations and we have not observed any significant variations during the course of the investigation. The few exceptions occurred in the severe cases of Group II b.

Short report on the numerical computations.—Computations of blood flow through the brain and the blood pool of the brain were made using

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two different methods. With the first method, use was made of the concentration curves obtained from the samples taken from the two bulbs, when labelled blood was injected once in the right and once in the left carotid artery. The theoretical formula used is correct provided the following conditions are fulfilled: (i) the injection is instantaneous, (ii) all activity reaches the brain, (iii) the blood is well mixed at the points where the samples are drawn and in the draining tubes, (iv) the two bulbs are the only outflows of the brain. Experience shows that conditions (i) and (iii) are quite well fulfilled. The other two conditions require a more careful analysis before one can be sure. It should be pointed out that the formula holds good independently of the number of inflows. The formula allows also for determination of the flow in each of the bulbs, and if one adds the assumption that there are also only two inflows to the brain one can also compute the flow in each of the carotid arteries. This determination will, however, probably not be as reliable as the determination of the total blood flow through the brain. The mathematical derivation of the formulæ can be found in an article by B. Andersson (1957). The formulæ are generalizations of formulæ given earlier by Hamilton *et al.* (1929).

The second method utilizes the concentration curves obtained from samples taken from one carotid artery and one bulb after making an intravenous injection. The formula is correct provided all the inflows show the same concentration curve and all outflows show the same concentration curve. There is no restriction on the number of inflows and outflows. This makes this method very attractive. The measurements must be very precise, since use is made of the difference between the concentration curves from the artery and the bulb, and this difference will be a small quantity. The accuracy of the present measurements seems to be sufficient for this purpose, except in a few cases. When we obtain samples simultaneously from one carotid artery and both bulbs the method is more exact. For a mathematical derivation of the formula, reference should be made to the above-mentioned work by Andersson. In the practical application of the formula it has been found possible to make the determination at a number of successive points along the curve and from these to determine a best mean value. This has increased the accuracy. One disadvantage of this second method, based on concentration curves obtained at the intravenous injection, is that it gives only the *ratio* of the blood flow and the blood pool for the brain, and not these quantities separately. This ratio is what has been called the turnover, or the inverted value of the mean circulation time, not exactly the same as that used by Hamilton. At present the formula has been used to compute the pool by combining it with the blood flow obtained from the first method. It would be of the greatest value to find a formula that would also give the blood flow directly from the intra-

venous experiment, since then both the blood flow and the blood pool would be correctly determined independently of the actual number of inflows and outflows. We have not succeeded in doing this yet, but are concentrating on the problem.

In some cases where not all the bulb curves could be obtained it was nevertheless possible to apply the formulæ to give the limits within which the blood flow value must lie.

The mathematical formulæ will be found in Table I.

TABLE I

$$\bar{q}_1 = \frac{I_1 \cdot C_{22} - I_2 \cdot C_{21}}{C_{11} \cdot C_{22} - C_{12} \cdot C_{21}} \qquad \bar{q}_2 = \frac{I_2 \cdot C_{11} - I_1 \cdot C_{12}}{C_{11} \cdot C_{22} - C_{12} \cdot C_{21}}$$

$\bar{q}_1$ denotes the outflow through the right jugular bulb in c.c./min.
$\bar{q}_2$ denotes the outflow through the left jugular bulb in c.c./min.
I_1 the total amount of injected activity in the right carotid artery in impulses/min.
I_2 the total amount of injected activity in the left carotid artery in impulses/min.
C_{11} the activity of the extrapolated surface of the dilution curve from the right jugular bulb injecting the right carotid artery in impulses/c.c.
C_{21} the activity of the extrapolated surface of the dilution curve from the left jugular bulb injecting the right carotid artery in impulses/c.c.
C_{12} the activity of the extrapolated surface of the dilution curve from the right jugular bulb injecting the left carotid artery in impulses/c.c.
C_{22} the activity of the extrapolated surface of the dilution curve from the left jugular bulb injecting the left carotid artery in impulses/c.c.

Total cerebral blood flow $= \bar{q}_1 + \bar{q}_2$

The pool of the brain $= \overset{+}{q}_1 \cdot T_1 + \overset{+}{q}_2 \cdot T_2$

where $\overset{+}{q}_1 = \dfrac{\bar{q}_1 \cdot \phi_{22} - \bar{q}_2 \cdot \phi_{12}}{\phi_{11} \cdot \phi_{22} - \phi_{12} \cdot \phi_{21}}$ and $\overset{+}{q}_2 = \dfrac{\bar{q}_2 \cdot \phi_{11} - \bar{q}_1 \cdot \phi_{21}}{\phi_{11} \cdot \phi_{22} - \phi_{12} \cdot \phi_{21}}$

$T_1 = \phi_{11} \cdot T_{11} + \phi_{21} \cdot T_{21}$ and $T_2 = \phi_{12} \cdot T_{12} + \phi_{22} \cdot T_{22}$

T_{11} the time co-ordinate of the gravity point of the dilution curve for right jugular bulb injecting right carotid artery
T_{21} the time co-ordinate of the gravity point of the dilution curve for left jugular bulb injecting right carotid artery
T_{12} the time co-ordinate of the gravity point of the dilution curve for right jugular bulb injecting left carotid artery
T_{22} the time co-ordinate of the gravity point of the dilution curve for left jugular bulb injecting left carotid artery

$$\phi_{11} = \frac{C_{11}}{I_1} \cdot \bar{q}_1; \quad \phi_{21} = \frac{C_{21}}{I_1} \cdot \bar{q}_2; \quad \phi_{12} = \frac{C_{12}}{I_2} \cdot \bar{q}_1 \quad \text{and} \quad \phi_{22} = \frac{C_{22}}{I_2} \cdot \bar{q}_2$$

The index $\dfrac{V}{q} = \dfrac{C_A - C_B}{C\infty}$ where $\dfrac{V}{q}$ is the relation between the pool of the brain V and the flow q. The latter one is derived from the first part of our calculation. C_A is the surface of the arterial dilution curve and C_B is the surface of the dilution curve from the bulb both simultaneously received after intravenous injection. $C\infty$ is the activity when equilibrium has been obtained after the injection.

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Angiography

In connexion with the isotope studies conventional carotid angiography was performed bilaterally; in some cases vertebral angiography also. Rapid serial angiography in both lateral and frontal projection was added, except in 5 cases when the examination had to be suspended for medical or technical reasons, and either no series (2 cases) or only a series on one side (3 cases) could be completed. The quantity of injected contrast medium was relatively small, being 4 ml. in the conventional angiographies and usually 5 ml. in the serial angiographies. 45–52·5 per cent Urographin was used. The contrast medium was injected by hand in the conventional angiographies but with a specially designed syringe in the serial angiographies. This syringe was coupled with the X-ray apparatus and the film-changers in such a way that a definite and constant time-relation existed between the start of injection and the exposures. The time of the injection and the exposures was recorded in some cases via a mingograph on a paper strip, together with the patient's ECG. This served as a check on the constant time sequence of the injection and the exposures and gave information of any changes of rhythm in the heart-rate during the investigation. It was only used in the last-mentioned cases.

The passage of the contrast medium through the blood vessels of the brain was in principle measured according to Greitz (1956). The circulation time was determined by fixing the time for maximum filling of the parietal veins. The passage through the arteries was determined by measuring the time of the emptying of the frontal and the parietal-occipital arteries respectively. In order to get a measurement which as nearly as possible correlates with the disappearance time obtained with the radioactive labelled erythrocytes, the time up to the maximum filling of the transverse sinus was determined. Moreover, the maximum filling and the emptying of certain individual veins was determined (Labbé's vein, the internal cerebral vein and the great cerebral vein of Galen). Greitz injected by hand and used the maximum filling of the siphon as starting point for his determinations. As automatic injection was used in the whole of the present material, all time determinations commenced with the starting of the injection. The injection time was 1·5 sec.

Procedure of the Examination

The investigation takes place in the X-ray department. The cases have been diagnosed clinically and are selected from the neurological clinic after careful consideration. The patient is placed on the X-ray table and may be given a suitable dose of morphine-scopolamine intravenously in order to produce relaxation. During the course of the investigation the blood pressure and pulse are plotted on a graph. After local anæsthesia the bulb puncture is performed high up on the neck

near the base of the skull. As a rule these punctures are quickly and successfully performed. Thereafter percutaneous puncture of the carotid arteries, if possible the internal carotid artery, on both sides is made. When the needles are inserted we first make an intravenous injection of labelled erythrocytes in an arm vein, this being done instantaneously within one second. At the same instant the sample-collector is put in operation and during the course of 60 seconds we collect the fractionated blood samples simultaneously, every second, from the two bulbs and one carotid artery. After this an exact quantity of labelled erythrocytes is injected first into one carotid artery and then into the other, and collection of blood from the two bulbs is immediately undertaken during the course of 30 seconds after separately injecting the right and the left carotid arteries.

Altogether, we generally collect samples from 7 different courses; 4 courses from the bulbs after injection of the two carotid arteries and 3 after the intravenous injection, i.e. simultaneously 2 from the bulbs and one from a carotid artery.

As a rule the investigation does not take very long. It could be done in half an hour, but it can be difficult to get the needle into a bulb and it can moreover be very difficult in the prevailing conditions to puncture the internal carotid artery percutaneously on both sides; often this does not succeed and the needle lies in the common carotid artery.

Material

We have examined 60 patients of whom 23 had to be excluded for technical reasons.

Group I comprises 18 patients without signs of cerebrovascular lesion; cases of epilepsy, old traumatic brain lesions and small cerebral tumours. 7 of these patients showed X-ray signs of atheromatosis of the cerebral arteries or pronounced brain atrophy, etc., and they were therefore transferred to a special Group (I b). The 11 remaining, relatively normal cases, which seemed to be free from arteriosclerotic cerebral changes, served as our control Group (I a). It is as a rule not possible to perform angiographic examinations in completely healthy persons even though today the risks are small.

Group II comprises 19 cases with signs of cerebrovascular lesion; practically all suffered from a hemiplegia which had occurred a few weeks or more before the circulatory investigation was performed. The cause of this vascular lesion could not be established with certainty through the clinical examination. However, severe acute strokes of the type of hypertensive hæmorrhage did not occur in the material. Nor were there any certain cases of cerebral embolism, although embolism can seldom be entirely excluded as the cause of a stroke.

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Through roentgenological examination a Group II b could be separated. In this group (6 cases) an occlusion or severe stenosis of the carotid arteries was found.

In the remaining 13 cases (Group II a) the cause of the stroke was undetermined and the angiography did not show any occlusion or severe stenosis.

Results

The first case in Group I a is a 27-year-old man with a probable diagnosis of epilepsy. In fig. 5 (152) can be seen two curves to the right and two to the left. Those on the left side represent the concentrations in the blood samples drawn from the right and left jugular bulbs in parts per thousand of the injected activity quantity in relation to the time which is stated on the abscissa in seconds after the injection in the right internal carotid artery. The two right-hand curves represent the concentrations of the drainage having regard to the time after the injection of the left internal carotid artery. The black dots represent the drainage on the same side as the injection and the open dots the contralateral bulb. Obviously the circulation in the brain is rapid. The first impulses from the labelled erythrocytes appear in the venous blood after only a few seconds following injection in the artery and the curves on the two sides are quite similar. We call these dilution curves. It is striking that the curve is higher and begins earlier on the injected side, whereas the curves from the contralateral bulb are lower and come later. If the injected quantity reaches the brain in its entirety and does not regurgitate into the common carotid artery and up into the external carotid artery, it should be possible to calculate mathematically the cerebral blood flow. In the case in question the latter amounts to 1,130 c.c./min. or 11 per cent of the cardiac output. It is also possible to calculate the blood pool of the brain. In the present case it is in round figures 100 c.c., i.e. 2 per cent of the total blood volume.

Through intravenous injection of labelled blood into an arm vein and the simultaneous taking of samples from a carotid artery and the two jugular bulbs, 3 dilution curves are obtained (fig. 5). The difference between the areas of the dilution curves of the artery and the bulbs gives the ratio between the cerebral blood flow and the blood pool in the brain or $\frac{q}{V}$, where q denotes the cerebral blood flow and V the blood pool of the brain; this can also be called the *turnover*, i.e. how many times a minute the blood pool is changed in the brain, in this case five times. The inverted value $\frac{V}{q}$ is the mean circulation time in the brain, in this case 0·211 min. or 13 sec. With the guidance of the mean circulation time obtained from the intravenous injection we are able to calculate the

blood pool of the brain by multiplying the cerebral blood flow—in this case 1,130 c.c./min.—by the mean circulation time, 0·211 min. We then get a blood pool of 238 c.c., which is more than twice as great as that obtained from calculations based on the four dilution curves from the carotid injections. It is not possible here to discuss the reasons for this difference.

The next case (106) concerns a 44-year-old man with a diagnosis of epilepsy. As can be seen from fig. 6, the curves were similar to those in the preceding case. The ipsilateral bulb drains more activity than the contralateral one. The disappearance time for the labelled erythrocytes through the brain, as in the preceding case, is 10 seconds. We have made calculations of the flow through the brain in this case and have arrived at a value, 1,200 c.c./min., very similar to that in the preceding case. In the present case this amounts to 15 per cent of the cardiac output (7·9 l./min.) which has been determined on the basis of the intravenous injection. The blood pool is estimated at 179 c.c. on the basis of the arterial injection. On the other hand, on the basis of the intravenous injection a somewhat lower value is obtained, 138 c.c. That is about 2·6 per cent of the total blood volume (5,980 c.c.). In this case the turnover—i.e. how many times the blood pool in the brain is changed per minute—is higher.

These 2 cases represent a small group of 3 cases where we have succeeded in carrying out bilateral punctures sufficiently high up in the internal carotid arteries and thus injecting the radioactive erythrocytes almost completely in the internal carotid artery with only an insignificant loss to the external area. The blood-flow determinations in these cases probably give a representative value. The third case had a blood flow of 880 c.c./min. The mean value for the cerebral blood flow is 1,070 c.c./min. for these cases. In this way it has been possible to estimate the cerebral blood flow in absolute values.

Various Circulatory Data

The statistics of the different functions have been worked out for the four different groups and are to be found in Table II. It will be seen that the mean age for the control group is 41 years, for Group I b—the intermediate group—52 years and for Groups II a+b—definite vascular lesions—56 years. On an average the heart volume is normal in all groups but there are some exceptions with larger hearts in group II a + b. The cardiac output is strikingly high, 10 l./min. in the control cases and this indicates that the patients were not entirely strictly resting, nor is it likely that they would be so in such a comprehensive investigation procedure. In the control cases the cerebral blood flow is high, 1,400 c.c./min., which, however, is only 12 per cent

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TABLE II.—MEAN VALUES FOR THE DIFFERENT FUNCTIONS IN THE CONTROL GROUP (I a), THE INTERMEDIATE GROUP (I b) AND THE VASCULAR GROUP (II a+II b)

Group	*Age*	*Weight kg.*	*Cerebral blood flow c.c.*	*Cerebral blood flow in % of cardiac output*	*Total blood volume c.c.*	*Heart volume c.c./m²*	*Cardiac output c.c./min.*
I a	41	73	1417±184 451 (6)	12·2±0·9 2·1 (6)	5241±159 528 (11)	366±22 72 (11)	10448±1240 4112 (11)
I b	52	71	1088±92 206 (5)	12·7±0·9 1·6 (3)	5011±508 1436 (8)	380±24 68 (8)	8285±1075 2404 (5)
II a+b	56	75	1272±97 443 (21)	17·4±1·5 6·3 (18)	4545±149 814 (30)	461±20 109 (30)	7879±382 1920 (25)

	Index $\frac{V}{q}$ *carot. inj. sec.*	*Index* $\frac{V}{q}$ *i.v. inj. sec.*	*Turnover* $\frac{q}{V}$ *carot. inj.*	*Turnover* $\frac{q}{V}$ *i.v. inj.*	*Pool* V *c.c. carot. inj.*	*Pool* V *c.c. i.v. inj.*
I a	7·3±0·9 2·6 (8)	7·5±1·3 4·0 (10)	9·4±1·4 4·0 (8)	10·6±1·9 5·9 (10)	155·2±29·7 66·5 (5)	177·0±40·2 89·9 (5)
I b	10·1±0·6 0·8 (2)	11·6±1·7 3·8 (5)	6·3±0 — (1)	5·8±1·8 3·1 (3)	151·0±65·0 91·9 (2)	251·3±47·8 82·8 (3)
II a+b	8·0±0·6 1·9 (11)	10·8±0·9 4·1 (21)	9·3±1·9 5·2 (8)	5·0±0·5 1·2 (7)	158·7±12·9 50·0 (15)	231·3±19·3 77·3 (16)

of the cardiac output. In the other groups, however, the blood flow is considerably lower, as one can see, 1,088 c.c. and 1,272 c.c./min., etc. In these cases the injections were done almost exclusively in the common carotid artery. For this reason, comparisons between the blood flow and blood pool of the two groups have no significance. It is uncertain if a connexion exists between the cardiac output and the cerebral blood flow, but this is something on which we cannot yet give an opinion and which we intend to investigate. The calculated values of the pool in the brain are higher when intravenous injection is used but are uncertain, as has been said before.

We consider the values in the 3 cases described above to be correct. Kety, Shenkin and Harmel (1948) are the only workers who have tried to estimate the cerebral blood flow (in 5 cases) by taking the average values for the drainage of the two bulbs, though when injecting Evans blue in the carotid artery on one side only. Kety and co-workers, using the N_2O method, and Lassen and Munck (1957), using radioactive krypton which is inhaled by the patient, blood samples being taken from one artery and the bulbs during ten-minute experiments, were able to determine the cerebral blood flow at between 50–60 c.c./100 grammes of the brain. But, as is well known, all brains are not of the same size. If, however, we assume a mean value of cerebral weight of 1,400 grammes, the flow of blood through the brain will be about 800 c.c./min. With our

method we arrive at a blood flow of something over 1,000 c.c./min. in the few cases where the injection was made in the internal carotid artery—in other cases rather more—and in individual cases we have obtained much higher blood flows—two litres and slightly over. This is probably due to the fact that the injected activity has not entered into the internal carotid artery to the full extent.

A more exact expression of the concentration of the labelled erythrocytes in the two bulbs is obtained by calculating the areas of the dilution curves that have been extrapolated before. We have related the areas to the amount of injected activity and obtain an index $\frac{c}{a} \times 1{,}000$, where c is the area of the bulb curve expressed in impulses and a the total injected activity (Table III). What we can venture to say today is that, generally

TABLE III.—SURFACE INDEX

	RIGHT ARTERY		LEFT ARTERY	
Group	*Right bulb*	*Left bulb*	*Right bulb*	*Left bulb*
I a	0·66±0·05	0·39±0·06	0·46±0·08	0·80±0·11
	0·16 (11)	0·20 (11)	0·23 (9)	0·34 (9)
I b+II a	1·19±0·10	0·60±0·08	0·69±0·07	1·17±0·10
	0·42 (18)	0·32 (18)	0·28 (17)	0·42 (17)

a=injected activity in impulses/min.
C=surface of curve in impulses.

$$\text{Surface index} = \frac{a}{C} \times 1000$$

DIFFERENCE BETWEEN THE VALUES FOR IPSILATERAL AND CONTRALATERAL BULBS

SURFACE INDEX

Group	*Injection right carotid artery*	*Injection left carotid artery*
I a	0·28±0·10	**0·34**±0·10
	(10)	(8)
I b+II a	0·59±0·07	**0·46**±0·08
	(17)	(17)

The values are: diff. ± error of diff. (degrees of freedom)
diff. in bold type=$p \leqq 0{\cdot}01$

speaking, nearly twice as many active erythrocytes flow out through the ipsilateral bulb as through the contralateral one, irrespective of whether the injection has been done in the right or the left carotid artery. The differences are in the main statistically proved by *t*-analysis.

We know that on injection of contrast into a carotid artery it is mainly the ipsilateral hemisphere which is filled. The venous outflow takes place through lateral, convexity and central veins. The former empty into the sagittal sinus and directly into one or both transverse sinuses. The central veins mainly empty themselves through the straight sinus.

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The outflow from the straight sinus and the sagittal sinus takes place both to the right and to the left transverse sinus. Therefore the bulbs cannot be entirely representative of the right and left hemispheres respectively. It is probable that the flow in the sagittal sinus may to some extent be laminar, so that the blood from one hemisphere mainly runs through the transverse sinus on the same side; still no laminar flow can be seen in the angiograms.

The circumstances here described probably explain the difference in types of curves and blood drainage between the ipsilateral and contralateral bulbs.

Our curves also give an insight into the circulation times in the brain. We can see when the first of the labelled erythrocytes have passed through the brain and appeared in the bulbs, the so-called "appearance time"; we can also see when they reach the maximum concentration, which we call the "peak concentration time"; and finally we can see when the labelled erythrocytes have practically all passed through the brain, the so-called "disappearance time." There is a clear tendency for appearance time and peak concentration time in general to be shorter on the ipsilateral than on the contralateral side of the injection, irrespective of whether the latter has been made in the right or the left carotid artery. The differences between the mean values for the different circulation times have been statistically proved by *t*-analyses in Table IV, and in

TABLE IV.—DIFFERENCE FOR CIRCULATION TIMES BETWEEN IPSILATERAL AND CONTRALATERAL BULBS

INJECTION RIGHT CAROTID ARTERY

Group	*Appearance time*	*Peak conc. time*	*Disappearance time*	*Interval*
I a	1·00±0·45	0·73±0·41	0·91±0·33	−0·91±0·46
	1·48 (11)	1·35 (11)	1·10 (11)	1·51 (11)
I b	0·17±0·40	0·33±0·62	−2·83±0·79	−3·00±0·97
	0·98 (6)	1·51 (6)	1·94 (6)	2·37 (6)
II a+b	**1·67**±0·31	**1·61**±0·42	0·39±0·63	−1·28±0·60
	1·33 (18)	1·79 (18)	2·66 (18)	2·54 (18)

INJECTION LEFT CAROTID ARTERY

Group	*Appearance time*	*Peak conc. time*	*Disappearance time*	*Interval*
I a	1·33±0·44	1·00±0·37	−0·44±0·44	−1·78±0·57
	1·32 (9)	1·12 (9)	1·33 (9)	1·72 (9)
I b	0·67±0·21	0·50±0·67	−0·33±1·75	−1·00±1·73
	0·52 (6)	1·64 (6)	4·27 (6)	4·24 (6)
II a+b	**1·41**±0·34	**1·05**±0·31	−1·59±0·78	**−3·18**±0·84
	1·59 (22)	1·43 (22)	3·63 (22)	3·94 (22)

The values are: mean diff. ± error, stand. dev. of diff. (number of cases)
diff. in bold type = $p \leqq 0{\cdot}01$.

TABLE V.—MEAN VALUES FOR CIRCULATION TIMES FOR THE TWO BULBS ON INJECTING RIGHT AND LEFT CAROTID ARTERY RESPECTIVELY, TOGETHER WITH CIRCULATION TIMES FOR THE ARTERY AND THE BULB AFTER INTRAVENOUS INJECTION

INJECTION RIGHT CAROTID ARTERY

	Appearance time		*Peak conc. time*		*Disappearance time*		*Interval app.-dis.*	
Group	*Right bulb*	*Left bulb*	*Right bulb*	*Left bulb*	*Right bulb*	*Left bulb*	*Right bulb*	*Left bulb*
I a	2·1±0·3	3·1±0·5	4·8±0·3	5·5±0·5	12·1±0·5	12·2±0·7	10·0±0·5	9·1±0·6
	0·8 (11)	1·8 (11)	1·0 (11)	1·8 (11)	1·8 (11)	2·2 (11)	1·7 (11)	2·1 (11)
I b	4·0±0·7	4·2±0·8	7·0±0·8	7·5±1·0	17·4±0·7	14·7±1·2	13·4±0·6	10·5±0·9
	1·8 (7)	1·9 (6)	2·1 (7)	2·4 (6)	1·9 (7)	2·9 (6)	1·7 (7)	2·3 (6)
II a+b	3·3±0·2	4·7±0·4	6·9±0·2	8·3±0·5	16·2±0·6	16·2±0·8	12·9±0·6	11·4±0·6
	1·0 (22)	1·8 (19)	1·2 (22)	2·2 (19)	2·7 (22)	3·5 (19)	2·7 (22)	2·5 (19)

INJECTION LEFT CAROTID ARTERY

	Appearance time		*Peak conc. time*		*Disappearance time*		*Interval app.-dis.*	
Group	*Right bulb*	*Left bulb*	*Right bulb*	*Left bulb*	*Right bulb*	*Left bulb*	*Right bulb*	*Left bulb*
I a	3·3±0·4	2·0±0·3	5·7±0·6	4·8±0·5	12·3±0·6	12·9±0·6	9·0±0·6	10·9±0·6
	1·3 (10)	0·9 (9)	1·8 (10)	1·4 (9)	1·9 (10)	1·9 (9)	1·8 (10)	1·8 (9)
I b	3·9±0·3	3·2±0·3	7·0±0·6	6·7±0·3	14·6±1·6	14·8±0·9	10·7±1·5	11·7±1·0
	0·9 (7)	0·8 (6)	1·5 (7)	0·8 (6)	4·2 (7)	2·2 (6)	4·0 (7)	2·4 (6)
II a+b	4·9±0·3	3·5±0·5	8·2±0·5	7·1±0·6	16·7±0·8	18·5±1·1	11·7±0·6	15·0±0·9
	1·7 (26)	2·2 (22)	2·4 (26)	2·8 (22)	4·2 (26)	5·0 (22)	3·2 (26)	4·3 (22)

INTRAVENOUS INJECTION

	Artery	*Artery*	*Artery*	*Bulb*	*Bulb*	*Bulb*	*Interval*
Group	*App. time*	*Peak c. time*	*Dis. time*	*App. time*	*Peak c. time*	*Dis. time*	*A peak–B peak*
I a	9·5±1·6	14·7±2·5	23·9±3·4	15·1±1·7	21·2±2·4	30·0±3·0	6·5±0·5
	5·2 (10)	7·9 (10)	10·6 (10)	5·5 (10)	7·6 (10)	9·5 (10)	1·6 (10)
I b	8·4±0·5	13·8±0·7	23·4±0·9	15·2±0·5	21·8±0·9	31·4±1·8	8·0±0·9
	1·1 (5)	1·6 (5)	2·1 (5)	1·1 (5)	2·1 (5)	4·1 (5)	2·0 (5)
II a+b	9·7±0·6	15·4±0·9	25·1±1·2	16·9±0·7	24·1±0·9	34·0±1·0	8·8±0·4
	3·2 (26)	4·7 (26)	6·0 (26)	3·6 (26)	4·8 (26)	5·0 (25)	2·1 (26)

TABLE VI.—STATISTICAL PROOF OF DIFFERENCE IN CIRCULATION TIMES BETWEEN GROUP I A AND GROUP II A+B

INJECTION RIGHT CAROTID ARTERY

Appearance time		*Peak conc. time*		*Disappearance time*		*Interval app.-dis.*	
Right bulb	*Left bulb*	*Right bulb*	*Left bulb*	*Right bulb*	*Left bulb*	*Right bulb*	*Left bulb*
1·23±0·35	1·65±0·69	**2·09**±0·41	**2·77**±0·77	**4·14**±0·90	**3·98**±1·17	**2·91**±0·89	2·33±0·89
(31)	(28)	(31)	(28)	(31)	(28)	(31)	(28)

INJECTION LEFT CAROTID ARTERY

Appearance time		*Peak conc. time*		*Disappearance time*		*Interval app.-dis.*	
Right bulb	*Left bulb*	*Right bulb*	*Left bulb*	*Right bulb*	*Left bulb*	*Right bulb*	*Left bulb*
1·59±0·59		**2·45**±0·83	2·36±0·99	**4·43**±1·38	**5·57**±1·72	2·69±1·08	4·07±1·49
(34)		(34)	(29)	(34)	(29)	(34)	(29)

The values are: diff.±error of diff. (degress of freedom).
diff. in bold type=$p \leq 0{\cdot}01$.

some cases turned out to be highly significant. This does not hold true of the disappearance time.

In Table V the mean values of appearance time, peak concentration time and disappearance time are tabulated for the three groups, viz. the control Group (I a), the intermediate Group (I b), and the cases with cerebrovascular disease (II a+b).

Appearance time, peak concentration time and disappearance time all increase systematically in Group II a+b, the group of cerebrovascular disease, in comparison with the control group. These differences between the two groups for appearance time, peak concentration time and disappearance time are highly significant, as is to be seen from Table VI. This prolongation of the circulation time in cerebrovascular disease is, of course, of great interest and it will be exemplified and discussed in what follows.

Clinical Applicability

The empirical analysis of dilution curve types gives obvious positive results. Here will be exemplified the correlation we have found between the dilution curves and the clinical and angiographic findings.

As an example from Group I b, the intermediate group, Case 108—a 58-year-old man suffering from epilepsy (fig. 7)—shows typical broadened dilution curves from the two bulbs on injection of the right carotid artery. Both the appearance time and, above all, the disappearance time are prolonged.

Group II a or cerebrovascular lesions (mostly hemiplegias) without roentgenologically demonstrable occlusions or severe stenoses, comprises 13 cases. All these cases, with one possible exception, have broad dilution curves with prolonged circulation times as a sign of retarded circulation in the brain. As an example can be taken Case 139 a (fig. 8), a 52-year-old man with moderate left-sided hemiplegia. The isotope-labelled erythrocytes appear late in the bulbs on injection in the left artery, not until about 7 sec. The affected side shows, on injection in the right internal carotid artery, very broad curves. The disappearance time for the two bulbs amounts to about 18 sec. in contrast to the mean value for the control cases of 12 sec. In conformity with the rule, the contralateral drainage is much less than the ipsilateral drainage. In this case, where obviously the injections of the labelled blood have been made in both internal carotid arteries, the calculations of the flow are probably quite reliable. The cerebral blood flow has been calculated at 1,140 c.c., i.e. 17 per cent of the cardiac output. The latter being computed on the basis of three bulb curves and a carotid artery curve on intravenous injection, as will be shown shortly. The four values for the cardiac output in this case vary between 6·7–6·2–6·6 and 7·1

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litres a minute, with a mean value of 6·7 litres. The same figure shows (139 b) the artery curve and three bulb curves after two intravenous injections. The close agreement between the three bulb curves is striking. They run practically parallel.

The next case (110), a 34-year-old man with moderate right hemiplegia and with slightly pathological neuroradiological findings, also shows (fig. 9A) broadened dilution curves, which were especially pronounced after injection in the left carotid artery. Both the ipsilateral and the contralateral bulb curves are broad, with considerable prolongation of disappearance time. On injection in the right carotid artery, also, the curves are broad and with prolonged circulation times. The patient improved during the ensuing months and when a second circulation examination was made six months later only a slight hemiplegia remained. In spite of the improvement, there are broad dilution curves on injection in the right carotid artery (fig. 9B). On the left side the needle was inserted at the bifurcation in the common carotid artery and probably most of the injected erythrocytes went up into the external carotid artery in accordance with the angiographic findings. At the first investigation we calculated the cerebral blood flow at 765 c.c. and the blood pool in the brain at 154 c.c., but the calculations are uncertain in this case.

Case 122 (fig. 10) is of special interest since it is the only case in this material where post mortem examination was performed. A 56-year-old man had previously (1957) had a heart infarct. In February 1959 he developed a left hemiplegia which at the time of the circulation examination in the middle of April had receded considerably. He shows broad dilution curves on injection of the carotid artery on both sides with prolonged circulation times including the appearance time. In September 1959 he developed a right hemiplegia and shortly afterwards he died. The autopsy showed bilateral brain infarcts and signs of a general arterio-arteriolosclerosis.

The next case (119) in the same group with slightly pathological X-ray findings is a 63-year-old man (fig. 11). In September 1958 he became weak in the right arm and leg and showed difficulty in writing and speaking. The neurological examination was negative at the time of the circulatory examination in April 1959. He nevertheless showed conspicuously broad dilution curves with long circulation times on injection in both carotid arteries; the dilution curves on both sides were very similar. The cerebral blood flow was determined at 820 c.c., i.e. 14 per cent of the cardiac output and the cerebral pool at 153 c.c. calculated on the basis of arterial injections and 240 c.c. calculated on the basis of the intravenous injection.

The last group, II b, represents cases where the diagnosis was occlusions or severe stenoses of the internal carotid artery, and comprises a comparatively small group, but one of great interest.

Case 115 (fig. 12A) is a 59-year-old man, who in February 1959 suddenly had a slight left hemiplegia. The angiographic examination showed total occlusion of the internal carotid artery at the neck bifurcation on the right side. The carotid siphon was filled with a minimal amount of contrast medium through collaterals via the external carotid artery and the ophthalmic artery. There was a marked stenosis of the left internal carotid artery. In this case the circulation through the brain via the carotid arteries was obviously greatly reduced. Therefore an injection of labelled erythrocytes in the vertebral artery was undertaken; the dilution curve from one jugular bulb was very high (fig. 12B). On calculating the flow on the basis of injection in the vertebral artery practically the same value was obtained (694 c.c./min.) as on injection in the stenotic left carotid artery, where it was calculated to be 730 c.c./min. As will be seen from the dilution curves, hardly any labelled erythrocytes are passing into the brain and out into the bulbs via the external carotid artery on the occluded side which illustrates the poor external collaterals in this case. Kety, who has carried out a few injections of dyes in the external carotid artery in normal cases, considers that a very small amount of dye passes into the bulbs; this is in agreement with what we have found. In certain pathological cases a collateral circulation is developed via the external carotid artery to the blood vessels of the brain. On injection in the common carotid artery on the left side the labelled erythrocytes pass via the brain in both hemispheres and are drained rather similarly in both bulbs. The contralateral dilution curve is, if anything, higher than the ipsilateral, in contrast to what we usually find in cases without total occlusion of the carotid artery. We have observed the same circumstance in similar cases. The dilution curves on the left stenotic side are extremely broad and the disappearance time is nearly twice that for the upper limit in control cases and is thus an expression of remarkably prolonged circulation in the brain. The appearance time also shows a prolongation.

The next case (135) in the same group, a 64-year-old man suffering from a hemiplegia, showed occlusions of both internal carotid arteries (figs. 13 and 14). Nevertheless it can be seen that on injection of the labelled erythrocytes in the left common carotid artery the erythrocytes pass into the brain and are drained into the bulbs; the appearance time, however, is very much delayed—8 sec.—and the disappearance time is very prolonged—at least 25 sec. Three weeks later the examination was repeated and strikingly similar dilution curves were obtained, thus constituting an example of the reproducibility of our dilution curves (138) (fig. 14). On the second occasion the appearance and disappearance times were even longer than on the first, being 11 and 30 sec. respectively. How is it possible that, in spite of bilateral occlusions of both internal carotid arteries, the labelled erythrocytes pass into the brain? The

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probable explanation is that a collateral circuit has been developed via the external carotid artery. That this was in fact the case was shown by the neuroradiological examination. With the intravenous injection on the latter occasion we obtained two not fully parallel dilution curves from both bulbs. The difference is very small, and may perhaps be explained by the error of the method for the time correction for the flow in the catheters. In such a grave case of circulation insufficiency in the brain as this, one would rather have expected a greater discrepancy between the drainage of the two bulbs.

The last case (159), a 68-year-old man who had two attacks of right-sided rapidly passing hemiparesis, showed total occlusion of the internal carotid artery on the left side and a considerable stenosis of the internal carotid artery on the right side (fig. 15). In conformity with the X-ray examination on the left side, some labelled erythrocytes pass via the external carotid artery up into the brain and are drained into the two bulbs, injection II in the figure. The circulation times are extremely prolonged and the appearance time is the longest we ever observed, namely 13 sec. This is probably due to the fact that at the moment of injection the blood pressure fell steeply to 70 mm.Hg against 150 immediately before. Shortly afterwards, the blood pressure rose again and an injection (III) was made in the right external carotid artery. Probably erythrocytes regurgitated up into the internal carotid artery in conformity with what was seen at angiography. The circulation times on this side also are considerably prolonged. Finally, a further injection (IV) was undertaken in the left common carotid artery; when the blood pressure had risen, prolonged circulation times were shown, but they were not nearly so prolonged as when the blood pressure fell to a remarkably low level.

Discussion

The use of labelled erythrocytes fulfils most of the physiological requirements for an indicator in studies of the circulation. The technique of sampling from the punctured bulbs seems to be correct and the sampling catheters do not change the dilution curves, as has been proved experimentally. The error in preparing the samples and measuring their activity is extremely small.

In order to test our mathematical calculations concerning flow- and pool estimations, we intend to use a mechanical model with several inflows and outflows whose diameter can be varied (as recommended by Sir Geoffrey Taylor).

Our experience up to the present has been that the theoretical formulæ give reasonable results. The blood pool computed, using dilution curves from the intravenous experiment, is usually somewhat larger than

the pool computed from the dilution curves in the carotid injections. Perhaps this may be explained by the fact that all inflows contain activity in the first case but not in the second case. Finally, there seem to be several possibilities of improving the mathematical calculations, and these should be tried out.

Kety and co-workers, on injecting dye into the freed carotid artery on only one side in 5 cases observed that complete mixing did not occur between the injected dye and the blood of the whole brain. They found that two-thirds of the dye supplied to the brain through the internal carotid artery of one side was drained through the ipsilateral bulb. Our investigations verify Kety's observations to the full. Kety also made an approximate calculation of the flow (on the basis of the injection of dye in the internal carotid artery of only one side) in the above-mentioned 5 cases and found a mean value of 986 c.c./min., which agrees fairly well with the value calculated by means of the nitrous-oxide technique for a mean weight of the brain of 1,400 grammes, namely 756 c.c./min. It should be mentioned that for these calculations Kety used an assumed brain weight. In their preliminary work, Nylin and co-workers, injecting labelled erythrocytes in the carotid artery on only one side, got similar values. In our present work, nevertheless, we have kept in mind that it was necessary to take account of the incomplete mixing between the indicator supplied and the blood of both hemispheres. Therefore, in this work on a large series, we consistently injected the labelled erythrocytes first in one and then in the other carotid artery. Unfortunately, it proved technically difficult to puncture the internal carotid artery percutaneously and therefore in most cases the blood-flow calculations were too high, owing to the fact that radioactive erythrocytes regurgitated out into the external carotid artery. However, we have control cases where the injections were made in the internal carotid artery and have calculated the cerebral blood flow to be 1,080 c.c.; this is probably accurate, especially if account is taken of the fact that the patients could not be examined under strictly resting conditions. Nobody has tried to estimate the blood content of the brain—the pool as we call it. Its calculation is in some degree uncertain and there are two different ways of calculating it. It is our hope that, with the model which is under construction, we may be able to solve the question why the results differ.

The dilution curves give an objective expression of the total circulation times in the brain. In the control group there does not seem to be any great variation in appearance time, peak concentration time or disappearance time. Further experience on a larger series of healthy subjects belonging to different age-groups is needed.

In general, the circulation time is shorter on the ipsilateral than on the

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contralateral side for appearance time and peak concentration time. It seems to be a characteristic sign in patients with cerebrovascular disease that the dilution curves are of different types from those of the control group. Appearance time, peak concentration and disappearance time are delayed, and the curves become broadened. These characteristics as a rule increase with the severity of the disease.

A sluggish blood flow is believed to give a tendency to cerebral anoxia in cases of atherosclerosis of the brain when the general blood pressure is reduced. Case 159 (fig. 15) is probably an extreme example of the effect of a fall in blood pressure. In this case the investigation with labelled erythrocytes was carried out as usual, immediately before the angiogram. During the former procedure there appeared a fall in blood pressure which lasted 3 to 4 min. An injection of labelled erythrocytes was made when the blood pressure was low; the injection was repeated shortly afterwards when the pressure had risen again.

Probably there was initially a slow blood flow, which was further greatly retarded when the blood pressure fell, the velocity of the blood flow rising again when the pressure increased. A deterioration of the blood supply to the brain in connexion with a fall in blood pressure, e.g. through a heart infarction, is commonly considered to be an important reason for the occurrence of cerebral infarctions. Denny-Brown and Meyer (1957) were able to investigate experimentally the development of infarctions, in connexion with a fall in blood pressure after arterial occlusion. In animal experiments they showed that an arterial ligature but little affected the circulation in the pial blood vessels (since a sufficient supply of blood took place via collaterals), but if the general blood pressure fell thereafter, there arose a slow blood flow in the pial vessels, sludging of the erythrocytes, œdema and finally a cerebral infarction. They considered that the circulation through the collaterals was specially sensitive to reductions of blood pressure.

The cerebral circulation times have also been determined by serial angiography. As a rule these times show the same tendency to changes of velocity in the examined pathological cases as those determined by the labelled cells. Furthermore, it was found that the velocity of the circulation through different parts of the brain was strikingly different, and was especially evident concerning the emptying of the veins. The differences often become more marked in pathological cases. Owing to the different velocities of circulation in different parts of the brain the drainage of the contrast medium from the transverse sinus becomes still more protracted and more difficult—even impossible—to follow. When the concentration maximum is measured in the transverse sinus, the circulation times measured are too short, and they are considerably

shorter than the total circulation time obtained with the labelled erythrocytes. The cerebral circulation times have been studied earlier with the contrast medium method by Moniz, Curtis (1949), Krayenbühl (1957) and Richter (1953), Greitz (1956), Schurr and Wickbom (1952), Tönnis and Schiefer (1959). The published times are highly dependent on the technique employed and sometimes vary considerably.

In Group I b, in which X-ray studies showed atheromatosis of the cerebral arteries, pronounced brain atrophy, etc., there were no clinical signs of cerebrovascular lesion. In several cases, however, there were rather long circulation times. This group thus offers findings of interest, although it is small and heterogenous. The prolongation of the circulation time measured with labelled erythrocytes may therefore indicate a deterioration of the cerebral circulation before any clinical signs of cerebrovascular insufficiency have appeared. This group is a special subject for our further studies.

Prolonged circulation times and broadened dilution curves are seen in Group II a, where the patients had shown clinical signs of insufficiency of the cerebral circulation. In Case 139 (fig. 8) which is an interesting case belonging to this group, the angiogram shows a very slow arterial circulation and very wide and tortuous arteries (the siphon and its bigger branches), but there are no narrowings and no demonstrable thrombosis of the larger arteries. The circulation times are prolonged and the dilution curve is rather broad. In this case with a normal blood pressure (and in the absence of an increased intracranial pressure) there is no other explanation of the slow circulation than an increased general cerebral "peripheral resistance," and this must be nearly equal in both hemispheres. We assume that this impeding factor may be located on the arterial side in the vicinity of the capillaries. The nature of the local or more general impeding factors is only partly known. There is, however, a high incidence of cerebral atherosclerosis in elderly patients who die from strokes, and this fact suggests that the slow cerebral circulation in Group II a is probably mostly connected with or caused by atheromatosis in the lesser arteries.

Concerning Group II b, several anatomical and circulatory aspects must now be further discussed.

As is seen from Case 123 (total occlusion of the right internal carotid artery + local but pronounced stenosis of the left internal carotid artery, fig. 16 A and B) and several other similar cases, one or more local narrowings of the internal carotid artery or its larger branches do not affect the velocity of circulation to a measurable degree (fig. 17, Plate XLIII); this is in full agreement with the investigations of Mann, Herrick, Essex and Balder (1938), who showed experimentally that the cross-sectional area of a blood vessel can be locally reduced by 70 per cent

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before observable change in the velocity of the blood flow takes place, when blood pressure is normal.

In Cases 115, 123, 135, 138, 159 (figs. 12, 16, 13, 14, 15) and others, there was occlusion of the internal carotid artery on one or both sides. In these cases collateral circulation occurs. This is in principle of three types: (1) Collaterals via the circle of Willis, i.e. between the hemispheres via the anterior communicating artery and between the carotid and vertebral sectors via the posterior communicating arteries. (2) Collaterals between the external carotid artery and the siphon via the ophthalmic artery. (3) The so-called peripheral or leptomeningeal collaterals between the main branches from the internal carotid artery or between these and the main branches from the vertebral arteries, such as via the posterior cerebral artery to the pericallosal artery and the middle cerebral artery (fig. 18 A, B, C, Plate XLIV). They were studied, especially anatomically, by Vander Eecken (1959) and also roentgenologically demonstrated by Schurr and Wickbom, Greitz, Krayenbühl and Yasargil and others. They are in most cases seen when one or both internal carotid arteries are occluded but are also observed in occlusion of smaller arteries, e.g. the middle cerebral artery. No case of this kind is included in this material. In Group II b (occlusions or severe stenosis) they are present in all cases with total occlusion of one or both internal carotid arteries which were completely examined, i.e. including vertebral angiography.

The circulation through the collaterals is sometimes, but not always, slow. If the anterior and posterior communicating arteries are well developed as well as other parts of the circle of Willis, the circulation through collaterals of type 1 will always be rapid. The collateral circulation of type 2 (through the external carotid artery) is often slow, sometimes very slow—cf. Case 159 (fig. 15). The circulation through the peripheral collaterals of type 3 is often relatively slow, but can be rapid as in case 115, where some parietal veins were filled more rapidly via peripheral collaterals from the basilar artery than normally via the internal carotid artery. A slow collateral circulation consequently accords with a prolonged circulation time for the dilution curve with labelled cells. In the same patient, normal circulation may occur through certain parts of the brain at the same time as considerably prolonged circulation is taking place in other parts. This results in a broadened dilution curve and a prolonged circulation time, i.e. the appearance time can be normal or almost normal, while the disappearance time is considerably prolonged. If the whole circulation in the brain was uniformly delayed, the appearance time and the disappearance time will be shifted to higher values, and the curves are more or less broadened. This exemplifies the theory that the dilution curve can be regarded as a summation or integration of several component curves.

Case 159 (fig. 15) (total occlusion of left internal carotid artery+very marked stenosis of right internal carotid artery) has a very rapid and well-functioning collateral circulation of type 1 through a broad anterior communicating artery; in serial angiography the arteries fill almost equally rapidly. But there is a considerable difference between the maximal filling of the parietal veins on the right and the left side. In this case, therefore, the supposed peripheral resistance seems to be very different in the two hemispheres. It is very difficult, and perhaps at present impossible, to obtain roentgenological evidence of more locally increased peripheral resistance. It is theoretically conceivable that local change gives locally prolonged circulation times both owing to slow circulation in peripheral collaterals and to locally increased peripheral resistance.

If the injury is below a certain order of magnitude, it does not reveal either anatomical or functional disturbances in the X-ray examination. On the other hand, the more sensitive method using labelled erythrocytes can give information. In these cases it is possible that the abnormal dilution curve represents the first objective symptom of cerebrovascular disease before neuroradiology is able to prove that anatomical or functional pathological changes are present.

On injection of labelled cells in the common carotid artery, with total occlusion of the internal carotid artery on the same side, different curves are obtained in different cases. Sometimes the curve is broadened and the circulation time prolonged; in other cases no labelled erythrocytes were obtained in the bulbs (Case 123, fig. 16). A satisfactory explanation of this is obtained through the X-ray investigation. The type of the dilution curve depends mainly on the function of the collaterals of type 2 (external collaterals). The external collaterals are probably only lacking in such cases where the whole siphon to the entrance of the ophthalmic artery has been obliterated and where consequently no anatomical conditions for external collaterals exist. In all cases of occlusion of the internal carotid artery, however, rapid serial angiography is necessary for the X-ray study, as the circulation through the external carotid artery can be greatly prolonged and therefore difficult to observe. In normal cases, blood probably does not pass from the external area to the brain, apart from the extremely small quantity which may pass through the "unworked" connexions from the external carotid artery to the siphon via the ophthalmic artery and other usually less significant collaterals, such as those between the external carotid artery and the vertebral artery (described by Richter, 1953).

Conclusions

In the great majority of cases the determinations of blood flow did not yield what we had hoped for at the beginning. It proved difficult to

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inject sufficiently high up in the internal carotid artery and to do so without a risk of regurgitation downwards into the external carotid artery. As a rule activity was lost into the latter, and to what extent this occurred it was impossible to determine in the individual case. Therefore, except in certain cases, the blood flow determinations are as a rule too high, and in consequence of this the blood pool values, i.e. the measured quantities of blood in the brain, are also too high. On the other hand, the results from the few cases where the injection was made sufficiently high up in the internal carotid artery seem reliable and accurate. In this way the cerebral blood flow was determined in absolute figures. It is remarkable that in all cases the blood flows, as a proportion of the cardiac output, are around 15 per cent, a value which may probably be regarded as reasonable.

Of the injected activity, twice as much is drained through the ipsilateral bulb as through the contralateral bulb. Our dilution curves give us clear information about the total circulation times in the brain, and they establish that the times are shorter for the ipsilateral than for the contralateral bulb.

In clinically diagnosed cases of cerebrovascular disease these curves were wholly divergent from those obtained in the control material. They are broadened, reflecting a prolonged circulation in the brain. The circulation times measured with labelled erythrocytes were also considerably prolonged in those cases where angiography could not show either occlusions or severe stenoses in the arterial system. The total circulation times are more exact than those obtained with angiographic methods. It is therefore possible that the method here outlined may in the future give valuable information from a diagnostic point of view.

The X-ray examination provides some possibilities for the interpretation of the dilution curves and the circulation times determined with labelled erythrocytes. (1) The different velocity of circulation through the different part of the brain both in normal and pathological cases. (2) The increased peripheral resistance, which may be general, half-sided and probably also more or less local. (3) The difference in the retardation factor in the different types of intracranial collaterals. (4) The varying function in the external collaterals.

It may perhaps be within the bounds of possibility to simplify the method. The technicians in the field in question consider it possible to capture the impulses bloodlessly via the bulbs; work on this project has already been started.

Summary

The blood circulation of the brain has been studied, using radioactive labelled erythrocytes which have been injected into the carotid arteries

on both sides, followed by simultaneous sampling of blood every second from the two jugular bulbs. The radioactivity of the samples has been determined and dilution curves plotted. Control cases show uniform and characteristic types of curves. In clinical cases of cerebrovascular lesions and arteriosclerosis quite different types of curves are found. The dilution curves also give the circulation times.

The method may prove sensitive for detecting certain cerebrovascular diseases. It may be possible to record the radioactive impulses bloodlessly over the bulbs.

Acknowledgments

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FIG. 1.—Sample-collector with three inflows.

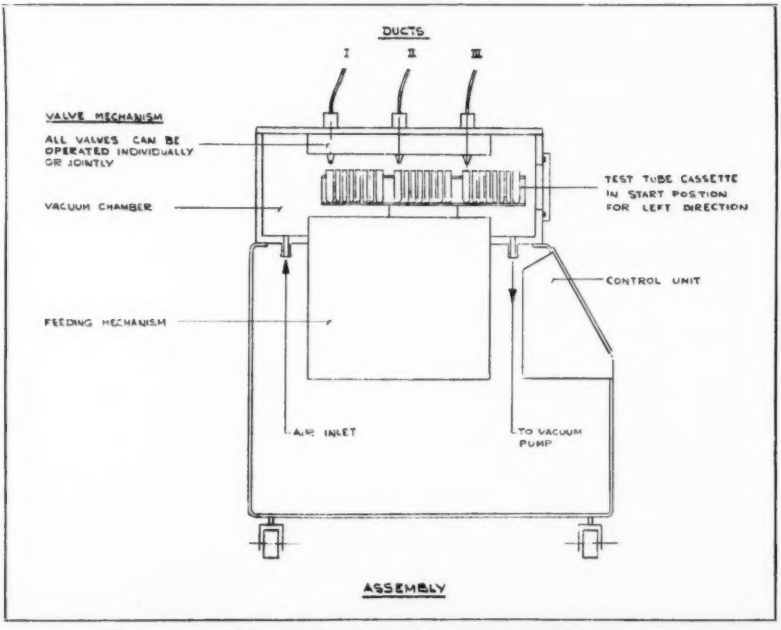

FIG. 2.—Schematic drawing of the sample-collector.

To illustrate article by G. Nylin, B. P. Silfverskiöld, S. Löfstedt, O. Regnström and S. Hedlund.

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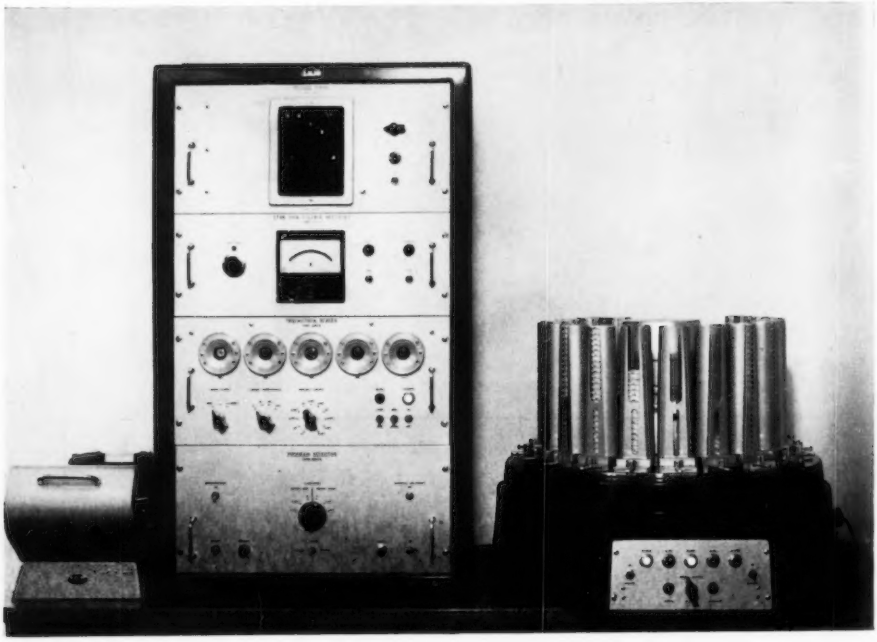

FIG. 3.—Right, sample changer; centre, robot scaler with Alfoén's trochotron decades; left, the computer.

To illustrate article by G. Nylin, B. P. Silfverskiöld, S. Löfstedt, O. Regnström and S. Hedlund.

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FIG. 4.

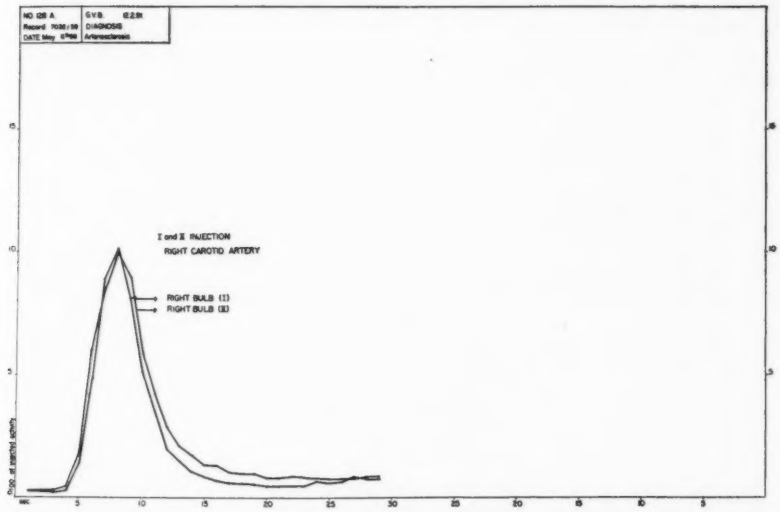

FIG. 4.—Dilution curves from the same bulb after double injection in the same carotid artery.

Case 128.—Male, aged 68.

Clinical findings.—During the preceding year he had shown progressive defects of memory and judgment. The gait was slow and shuffling. The neurological examination showed otherwise normal conditions. Blood pressure 240/160. Diagnosis: Cerebral arteriosclerosis?

X-ray findings.—Arteriography in right common carotid artery. Percutaneous injection of 45 per cent urographin. No changes in the internal carotid artery in the neck. The suprasellar part of the carotid siphon had a slightly irregular lumen. The lumen in a few blood vessels of the Sylvian group was somewhat irregular. One of the main branches had a somewhat wider lumen than the others. The examination was incomplete (suspended owing to patient's condition).

Arteriography in the left common carotid artery. Percutaneous injection of 45 per cent urographin. Only neck picture taken. No changes in the internal carotid artery. Examination suspended.

FIG. 5.

Case 152.—Male, aged 27.

Clinical findings.—On August 23, 1959, he had a *grand mal* seizure, probably preceded by myoclonus.

The neurological and ophthalmological examinations showed no abnormality.

EEG: normal.

Blood pressure: 150/100.

Diagnosis: Epilepsy?

X-ray findings.—Internal carotid angiography (bilateral) showed no abnormalities and encephalography revealed slightly wide lateral ventricles on the

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left side. Rapid serial angiography—normal circulation times. In this case the internal carotid vein and the vein of Galen contained contrast medium 2–3 sec. after the parietal veins were empty.

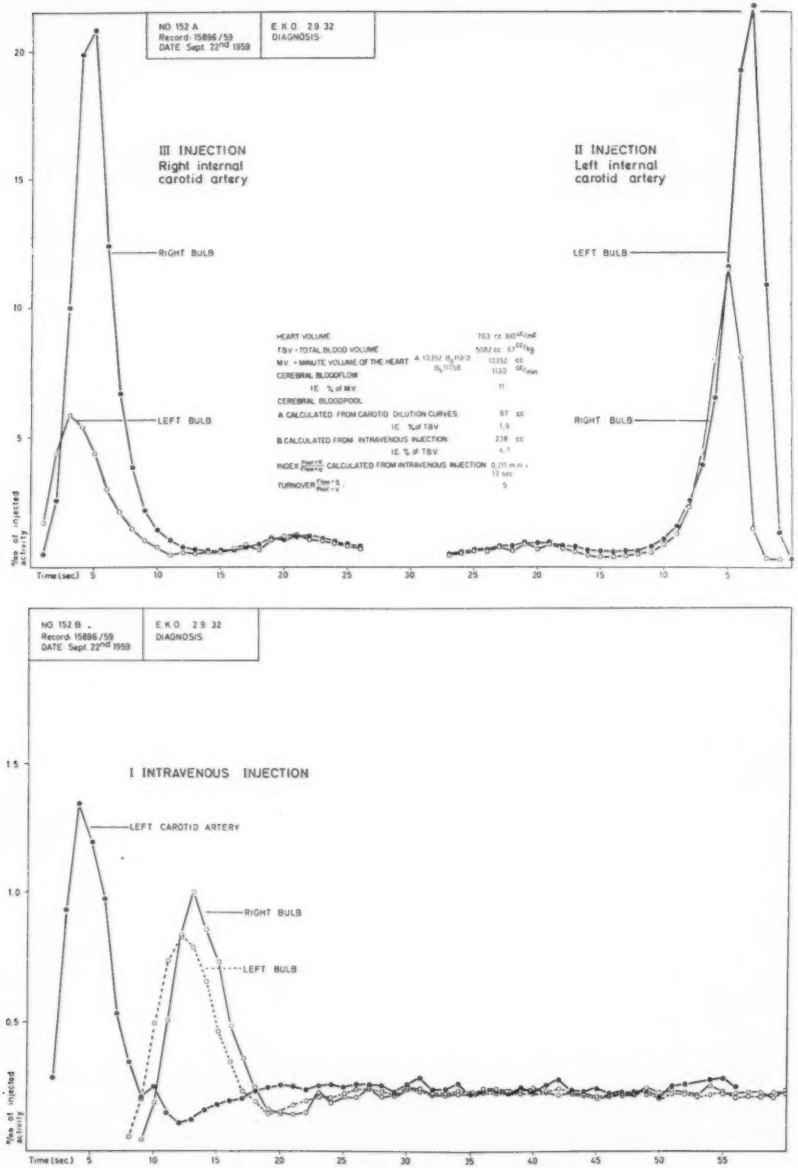
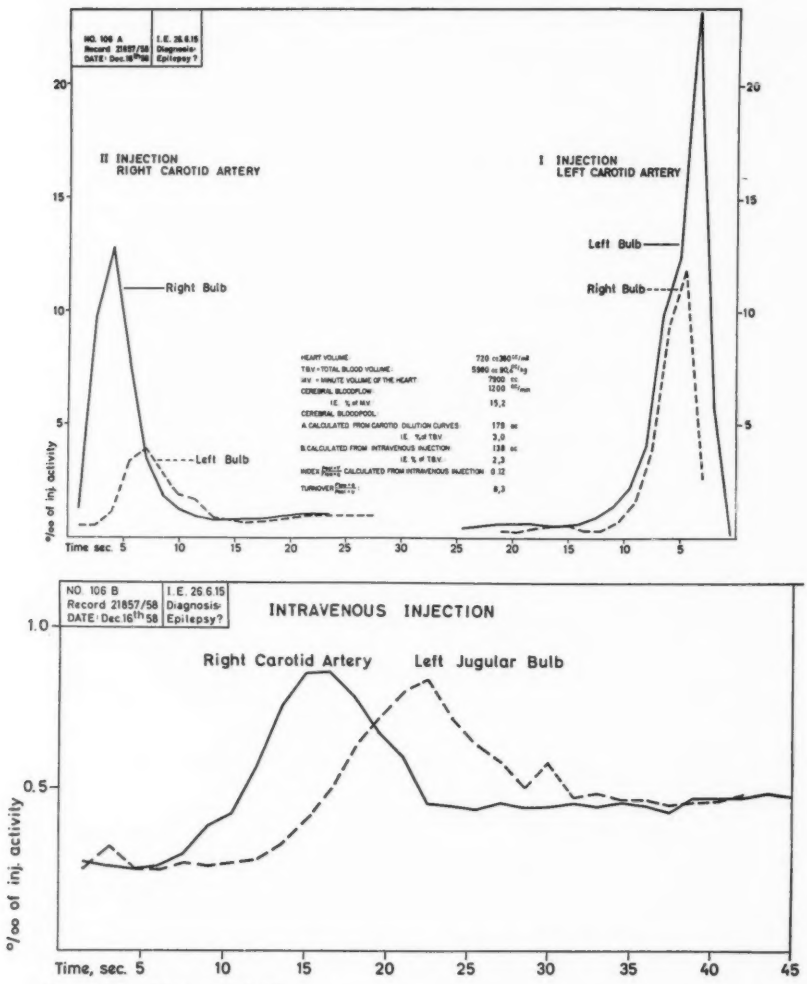


FIG. 5.

FIG. 6.



Case 106.—Male, aged 44.

Clinical findings.—In December 1958 and January 1959 he had sudden fits of unconsciousness preceded by very short vertigo.

Neurological and ophthalmological examinations showed no abnormality.

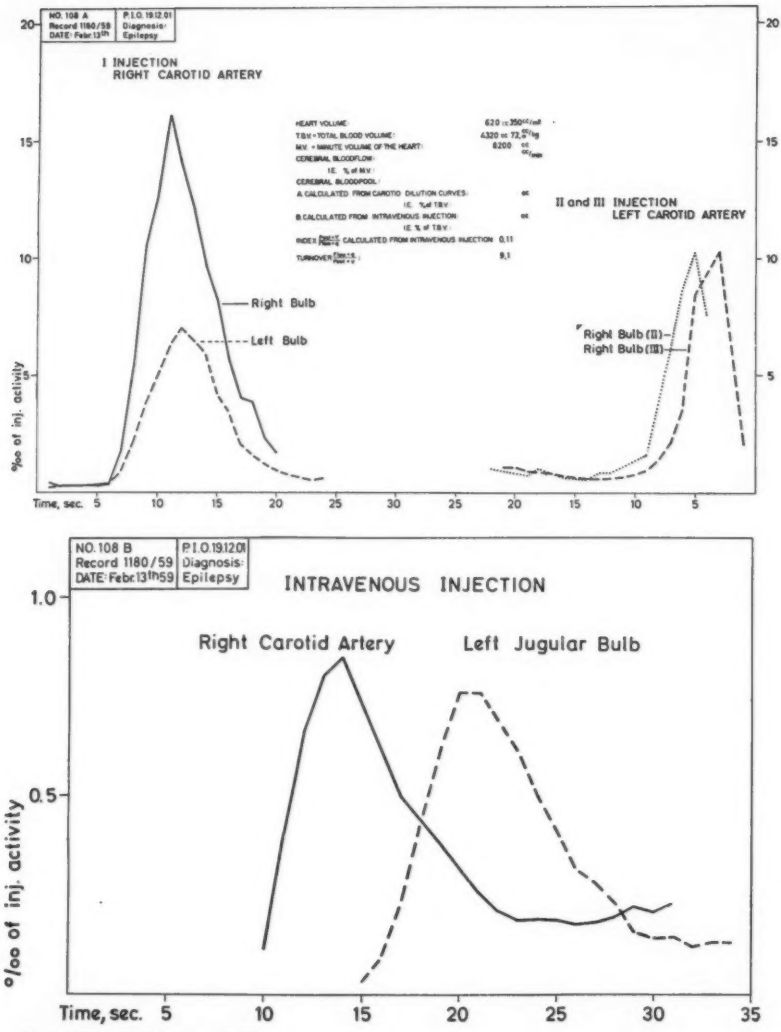
EEG: neuronal hyperexcitability; no focal pathological activity.

Blood pressure: 120/80.

Diagnosis: Epilepsy?

X-ray findings.—Internal carotid angiography bilaterally showed no abnormalities and encephalography slightly wide lateral ventricles. Normal circulation time on rapid serial angiography.

FIG. 7.



Case 108.—Male, aged 58.

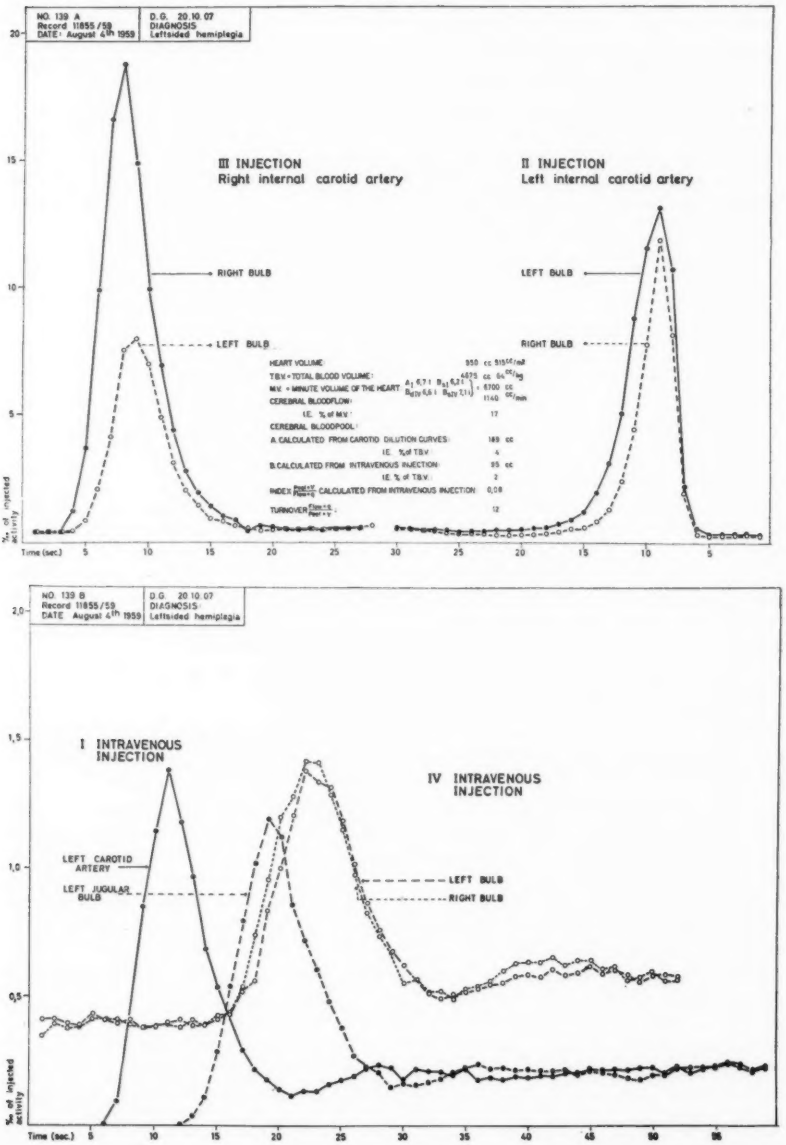
Clinical findings.—Since 1949 he had suffered from seizures characterized by speech disturbances followed by confusion or unconsciousness. The neurological and ophthalmological examinations showed no abnormality.

EEG: epileptogenic activity from the anterior part of the left temporal lobe. Diagnosis: Epilepsy.

X-ray findings.—Common carotid angiography bilaterally showed rather wide and tortuous arteries without narrowings. In rapid serial angiography, the

contrast passage through the arteries, especially on the left side, was slow (5 sec.). The circulation time—up to maximum filling of the transverse sinus—was not noticeably prolonged. Encephalography showed slightly wide lateral ventricles.

FIG. 8.



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Case 139.—Male, aged 52.

Clinical findings.—On June 26, 1959, a slight weakness of the left arm appeared and on the following day he developed paralysis of the arm and a moderate weakness in the left leg. When the study of the cerebral circulation was performed a considerable improvement had occurred.

Ophthalmological examination normal.

Blood pressure: 170/100 mm.Hg.

Diagnosis: cerebrovascular lesion.

X-ray findings.—Internal carotid angiography bilaterally showed wide and tortuous arteries without narrowings and in rapid serial angiography the contrast passage through the arteries was much prolonged (7–8 sec.) on both sides. The circulation time up to maximum filling of transverse sinus was prolonged. Encephalography showed a very marked atrophy bilaterally (max. width of the lateral ventricles (40–45 mm.). No other abnormalities.

FIG. 9.

Case 110.—Male, aged 34.

Clinical findings.—In December 1958 he developed a weakness in the right arm and leg of a few days' duration. One month later these symptoms reappeared and on the patient's admission (January 1959) to the neurological department there was a moderately severe right hemiplegia with increased reflexes; there was a pronounced sensory loss in the same side; when the first circulatory investigation was performed (three weeks after the second cerebral accident) the symptoms had diminished slightly. There was a homonymous right upper quadrantanopia.

EEG: a slight non-specific pathological activity over the left temporal region.

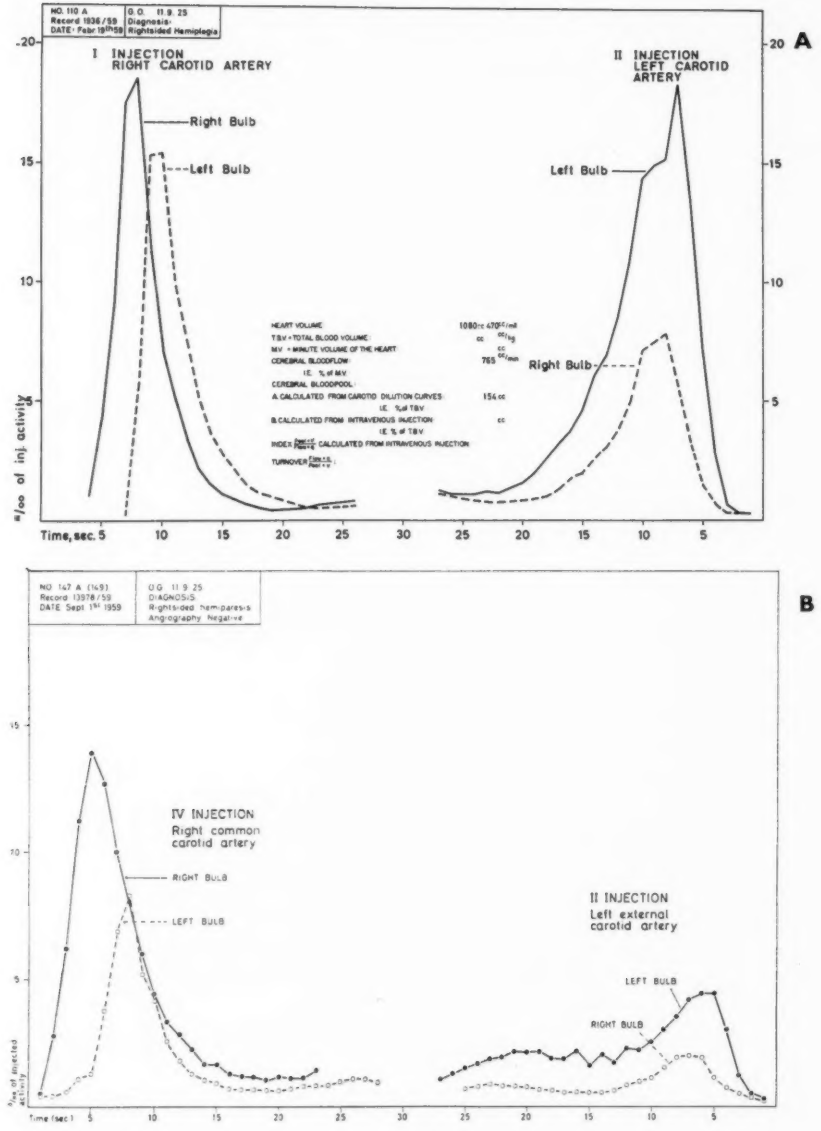
Blood pressure: 165/115.

During the following months the patient improved considerably. However, a slight hemiplegia and a rather conspicuous loss of position sense in the right arm remained, at the time of the second circulatory examination.

X-ray findings.—Common carotid angiography bilaterally in February 1959 showed a very slight shift of the pericallosal arteries and the internal carotid veins to the right. No other abnormalities. The total circulation time up to the maximum filling of the transverse sinus was rather long (at least 9 sec.) on both sides and the arterial circulation time on the left side was a little delayed. On encephalography, a shift of septum pellucidum and the third ventricle was found corresponding to the asymmetry of the arteries and central veins but more pronounced.

Common carotid angiography bilaterally and encephalography seven months later showed quite normal anatomical conditions. Only the arterial circulation in the left hemisphere was, as at the first examination, rather slow. It could now be concluded that the small changes shown at the first examination had been caused by an expanding process, probably a vascular lesion in the left hemisphere.

In this case there were no X-ray symptoms of arteriosclerotic changes in the arteries.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I INJECTION
RIGHT CAROTID ARTERY
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IV INJECTION
Right common
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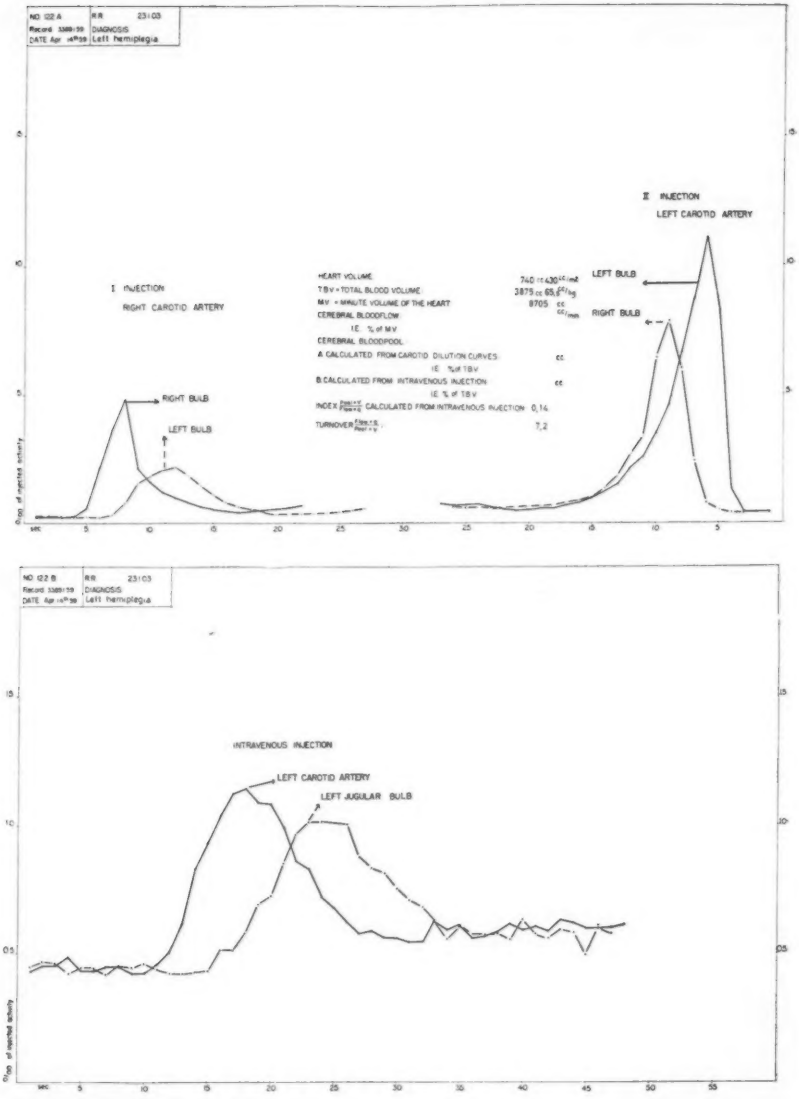
FIG. 9.

FIG. 10.



Case 122.—Male, aged 56.

Clinical findings.—In 1957 there were signs of a cardiac infarction. On February 18, 1959, he rather rapidly developed a paralysis of the left side (mouth, arm and leg).

At the time when the cerebral circulation was examined there remained a moderately severe hemiparesis. The patient slowly improved but on September 6 he got a right-sided hemiplegia and died a week later, September 13.

EEG: marked pathological activity over the right frontal region.

Ophthalmological examination: normal.

Blood pressure: 150/100.

Necropsy:

Brain: in the right hemisphere, mainly in the parietal lobe, there was an old cystic infarction; a recent infarction was found in the left parieto-temporal region.

Kidneys: several old infarctions. No changes in the renal vessels.

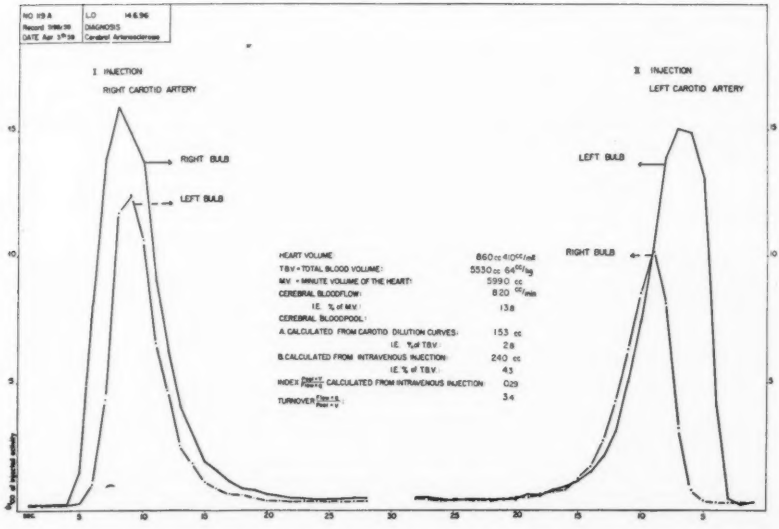
Heart: an old infarction was found in the posterior wall; only very slight arteriosclerosis was present in the coronary arteries.

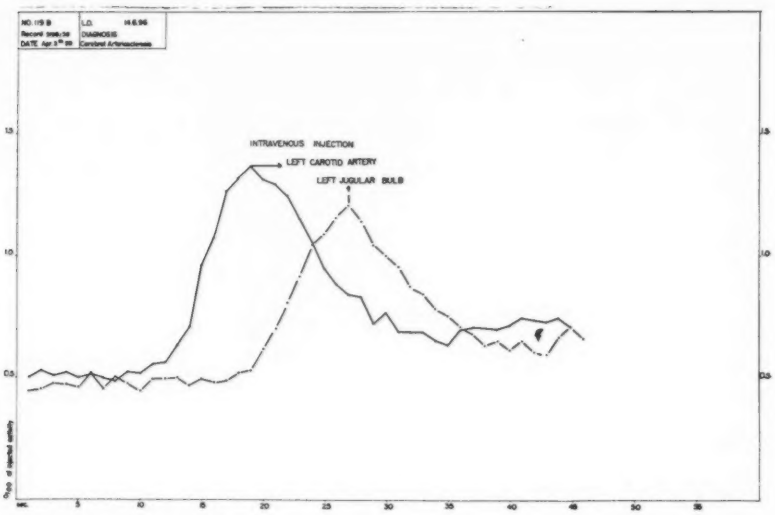
Unfortunately the brain was not preserved for a microscopic study. Numerous sections from the heart, kidneys, suprarenal bodies, liver, spleen and lungs were examined. In the small arterial branches and arterioles there was a very pronounced arterio-arteriolosclerosis with marked thickening of the intima and narrowing of the lumen. No total occlusions were seen.

Diagnosis: Cerebrovascular lesion.

X-ray findings.—Common carotid angiography bilaterally showed only very slight local intimal thickenings in the left siphon but no other abnormalities. The circulation time up to maximum filling of the transverse sinus was rather long (9·5 sec.).

FIG. 11.





Case 119.—Male, aged 63.

Clinical findings.—In 1945 and 1956 he had fits of unconsciousness of uncertain origin. In September 1958 he became slightly weak in the right arm and leg with some difficulty in speaking and writing. No definitive residual defects were present on his admission to the neurological department in March 1959.

Ophthalmological examination: slight hypertensive neuroretinopathy.

EEG: normal.

Blood pressure: 180/105.

Diagnosis: cerebrovascular lesion.

X-ray findings.—Common carotid angiography bilaterally showed small intimal thickening in the cervical part of the internal carotid arteries and in the right siphon, which was slightly narrowed. No other arterial abnormalities. The total and arterial circulation was rather slow, but within normal limits.

FIG. 12.

Cases 115 *and* 118.—Male, aged 59.

Clinical findings.—In February 1959 there appeared a sudden, slight left-sided hemiplegia which increased during the following days. On admission to the neurological department a few weeks later he showed a pronounced hemiplegia of the classical type and a moderate dementia.

The examination of the brain circulation was performed somewhat later, at which time a slight improvement of the neurological symptoms had taken place.

Diagnosis: Cerebrovascular lesion.

X-ray findings.—Common carotid angiography bilaterally: the right internal carotid artery was totally occluded close to the neck bifurcation (division of the common carotid into the internal and external carotid arteries). There was

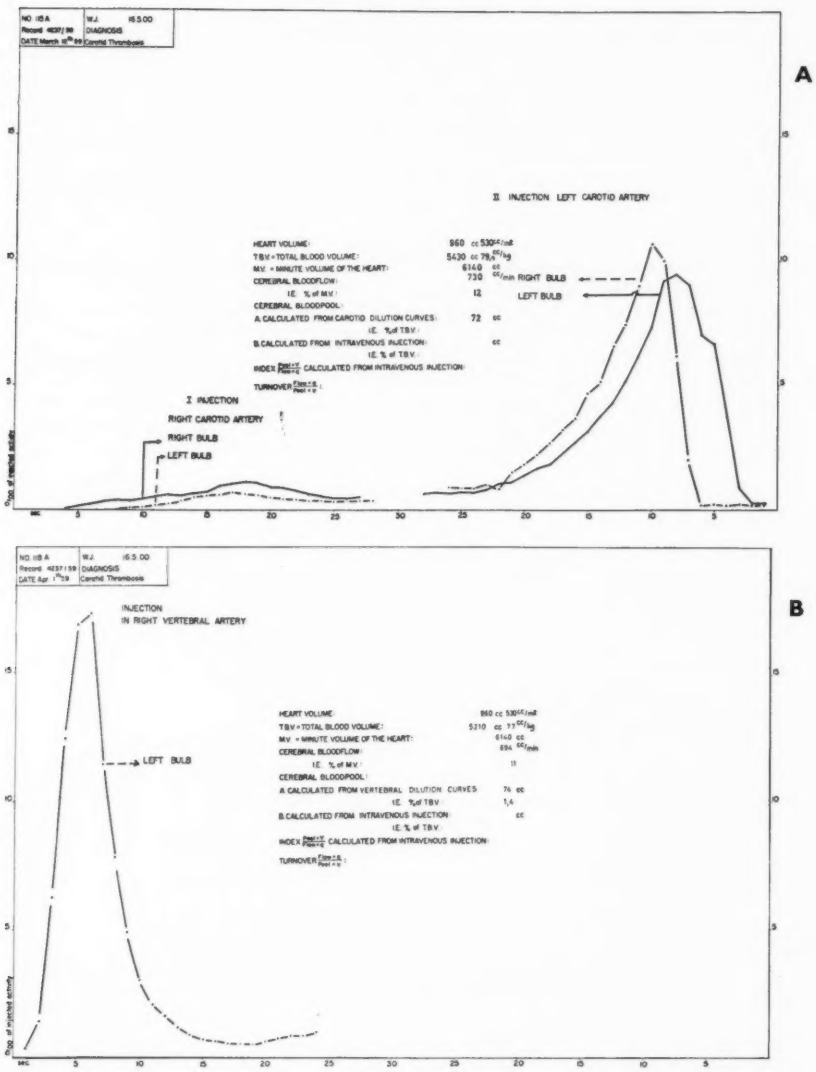


FIG. 12.

a very poor filling of the siphon from the external carotid artery via retrograde filling of the ophthalmic artery. Only a few branches of the pericallosal and middle cerebral arteries were filled. On injection in the left common carotid artery the pericallosal and middle cerebral arteries in the right hemisphere were filled via the anterior communicating artery in the circle of Willis. The filling was not optimal

by this route. On vertebral angiography there was rather good filling of some of the carotid branches via the posterior communicating artery. Besides these three collateral ways—(1) via the external carotid artery, (2) the anterior and (3) the posterior communicating arteries—there was a fourth collateral pathway via peripherical or leptomeningeal anastomosis because contrast passed by vertebral angiography from the small peripheral branches of the posterior carotid artery to the pericallosal and middle cerebral arteries on the right side. Thus the pericallosal artery filled in retrograde direction almost to the level of the genu of the callosal corpus. In this way the peripheral arteries in the parietal and temporal regions were filled with contrast medium. This collateral circulation was rather rapid and the parietal veins filled via these peripheral collaterals in only 3–4 sec., i.e. with greater rapidity than the ordinary way via the siphon. Thus in this case there was a complete occlusion of the cervical part of the right internal carotid artery. The right hemisphere was nourished by 4 collateral systems: (1) a poor and slow circulation via the external anastomosis to the siphon, (2) and (3) the anterior and posterior communicating arteries from the left internal carotid artery and the vertebral artery and (4) peripheral or leptomeningeal anastomosis between the posterior cerebral artery on one side and the pericallosal and middle cerebral arteries on the other. Encephalography was not performed, but on the phlebogram a moderate dilatation of the ventricles could be seen.

FIG. 13.

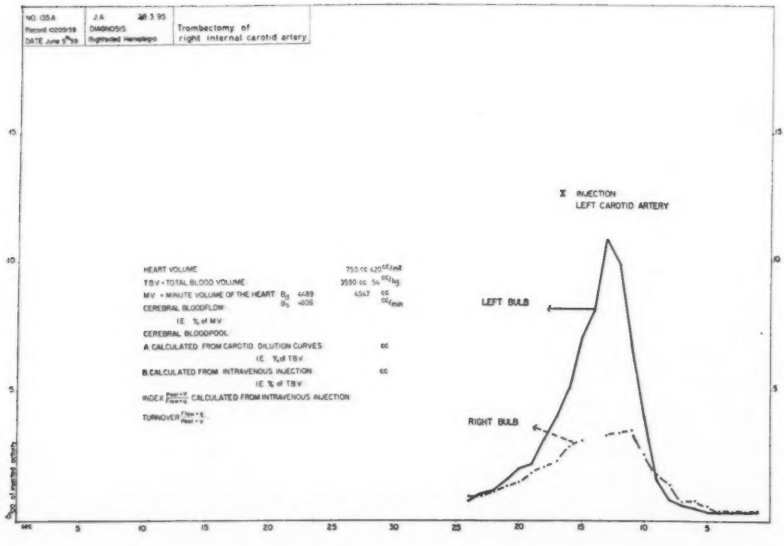
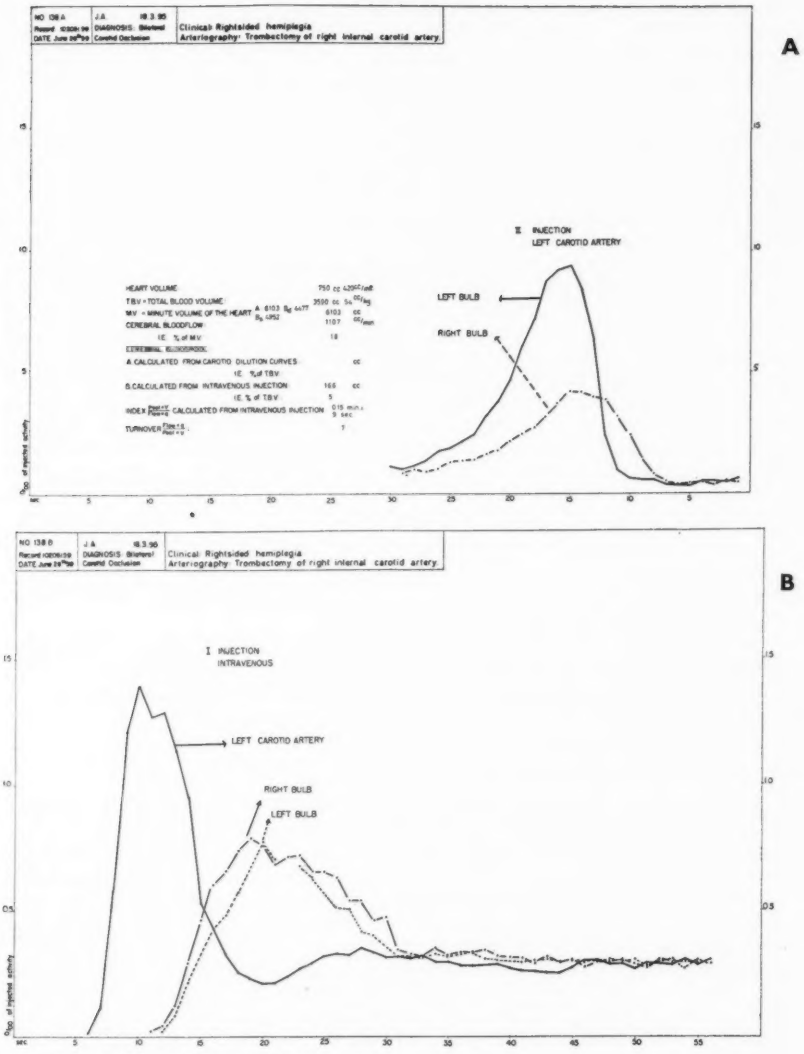


FIG. 14.



Case 135, 138.—Male, aged 64.

Clinical findings.—He had suffered from cardiosclerotic symptoms and intermittent claudication for several years. On January 1, 1958, he developed a right hemiplegia and aphasia. On May 7, 1958, a thrombendarterectomy was performed in the right carotid artery. The symptoms were worse immediately after this operation but thereafter he improved slightly. The following year there remained a

moderately marked aphasia and hemiplegia. The effects of the operation were checked by an examination of the cerebral circulation. However, puncture of the carotid arteries succeeded only on the left side.

Ophthalmological examination: normal.

EEG: marked non-specific pathological activity over the left temporal region.

Blood pressure: 170/100.

Diagnosis: cerebrovascular lesion.

X-ray findings.—This patient had a complete occlusion of the cervical part of the right internal carotid artery. Thrombectomy was performed but did not lead to restoration of the circulation. In addition there was a complete occlusion of the left cervical part of the left internal carotid artery. On the left side there were relatively well functioning external collaterals to the siphon although the external main vessel was moderately obstructed close to the neck bifurcation. In this way the pericallosal and the posterior cerebral arteries, but not the middle cerebral artery on the left side, were filled. The circulation through these vessels was greatly prolonged. The pericallosal and the middle cerebral arteries on the right side were filled via the anterior communicating artery. The filling of the vessels in both hemispheres was, however, incomplete. From earlier examinations it was evident that there was no collateral circulation through the external branches on the right side. Thus the bigger branches of both the internal carotid arteries were filled only via the left external collaterals to the siphon. On vertebral angiography many branches belonging to the pericallosal and middle cerebral artery on both sides were filled via peripheral collaterals from the posterior cerebral arteries.

FIG. 15.

Case 159.—Male, aged 68.

Clinical findings.—On July 26, 1959, and August 6, 1959, there occurred short attacks of hemiparesis in the right arm and leg.

The neurological and ophthalmological examinations showed no abnormality.

EEG: non-specific pathological activity over the left hemisphere.

Blood pressure: 150/70.

Diagnosis: cerebrovascular lesion (ischæmic attacks?).

X-ray findings.—Common carotid angiography bilaterally revealed complete occlusion of the cervical part of the left internal carotid artery and a 2–3 cm. long, rather marked annular narrowing of the right internal carotid artery beginning close to the neck bifurcation. On the left side there was a poor collateral circulation via external branches to the ophthalmic artery and the siphon. From these collaterals only the posterior cerebral artery was filled. The circulation was very slow, the filling of the siphon beginning after 4 sec. (normally $<0{\cdot}5$ sec.). On the right side the circulation, despite the marked narrowing of the internal carotid artery, was only very slightly delayed (filling of the siphon after 0·5–1 sec.). From the right siphon the anterior cerebral, pericallosal and middle cerebral arteries on both sides were filled (collateral circulation through the anterior communicating artery). The difference in time in the filling of the arteries on both sides is rather small, only 0·5–1 sec., but the max. filling of the parietal veins was greatly delayed on the left side (right—5 sec., left—10 sec.). As contrast medium from both sides is mixed in the transverse sinus the max. filling of this is not representative of either of the hemispheres. The filling of the middle cerebral arteries is very asymmetrical, the arterial tree on the right side has remarkably more branches than on the left. The two

pericallosal arteries are more symmetrical and there is evidence of peripheral or leptomeningeal anastomosis between the left pericallosal artery and the left middle cerebral artery. Vertebral angiography was not performed.

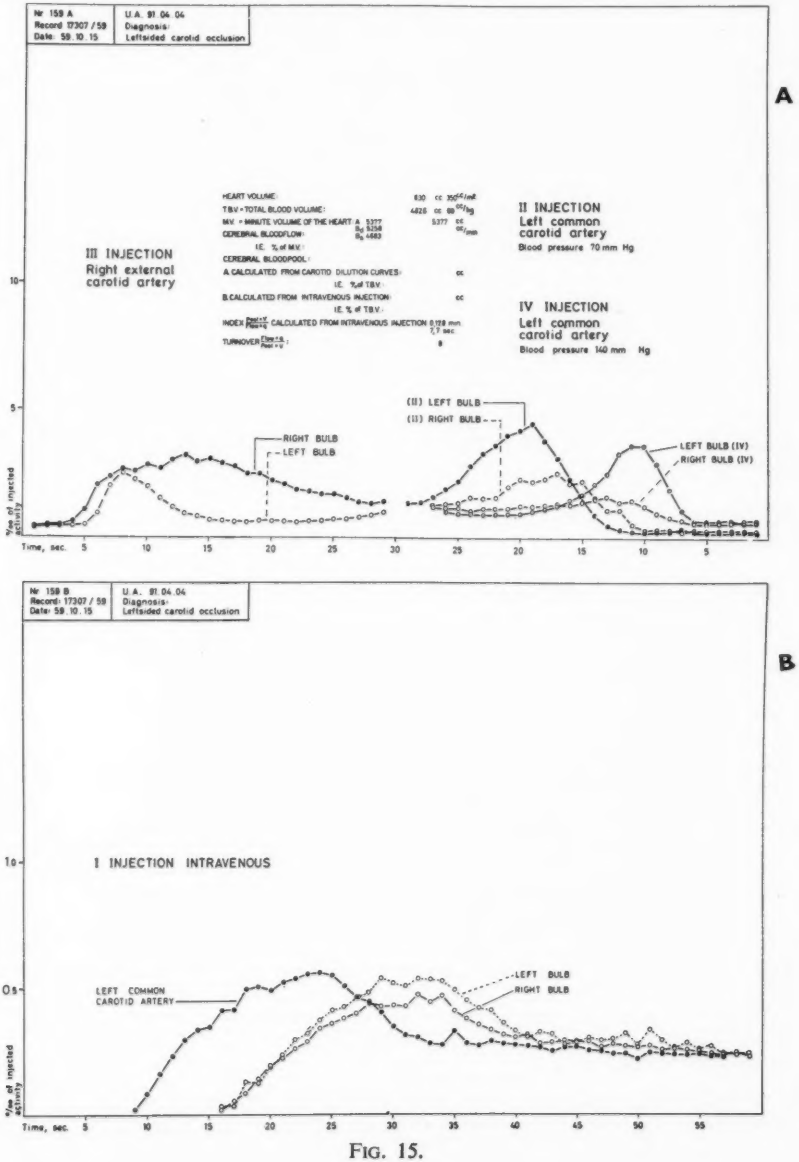
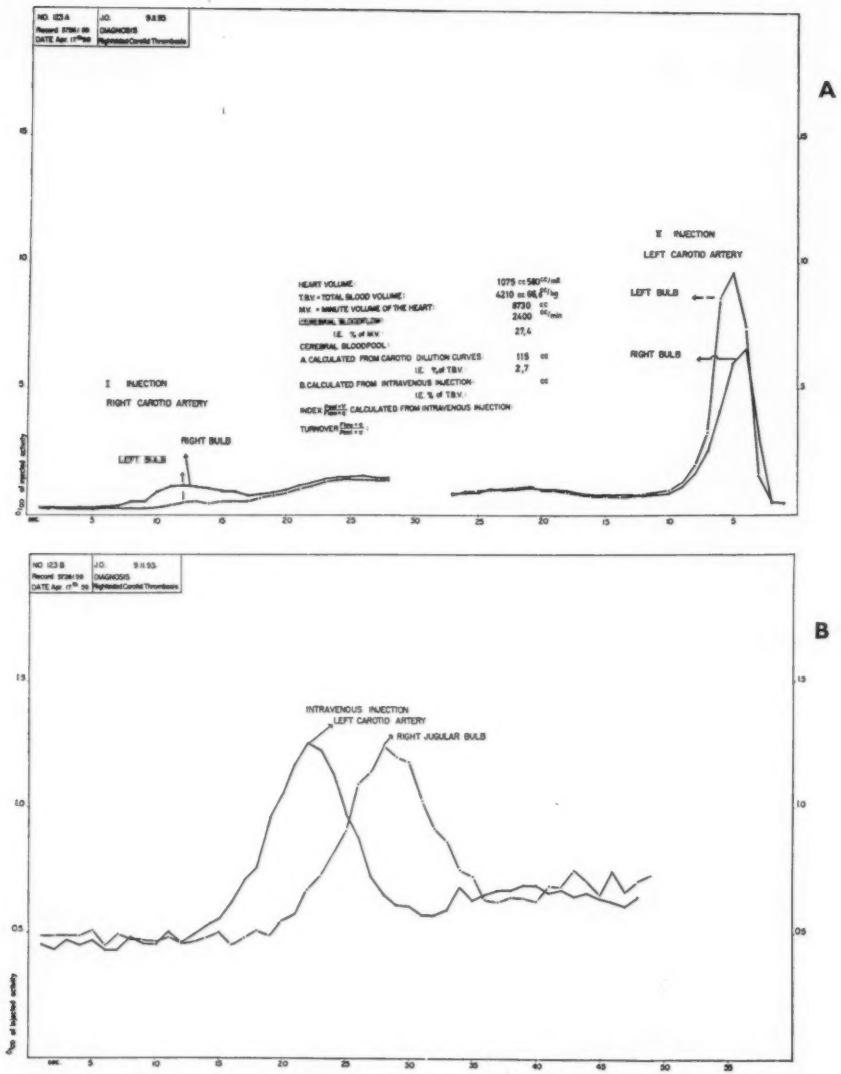


FIG. 15.

FIG. 16.



Case 123.—Male, aged 66.

Clinical findings.—In March 1959 a slight left-sided weakness appeared. He was admitted to the hospital the same day; there was a moderate weakness in the left

arm, a slight weakness in the left leg with a positive Babinski sign. He recovered completely after a few days.

Blood pressure: 190/110.

Psychometric tests showed no signs of dementia.

Diagnosis: Cerebrovascular lesion.

X-ray findings.—Common carotid angiography bilaterally: local but very marked narrowing of the cervical part of the left internal carotid artery close to the neck bifurcation and of the para- and suprasellar parts of the siphon. The intracranial branches rather wide and tortuous. The circulation times normal despite the multiple very pronounced narrowings of the internal carotid artery. On the right side there was a (complete) occlusion of the internal carotid artery close to the neck bifurcation, without collateral circulation to the siphon via external branches. No other collateral circulation from the external carotid artery could be seen. Vertebral angiography showed very marked multiple narrowings in the vertebral and basilar arteries. Via the posterior communicating artery contrast passes to the right siphon and further to the middle cerebral artery. The right pericallosal was not filled this way but via the anterior communicating artery from the left internal carotid artery. The circulation time to maximal filling of the parietal veins via the vertebral artery—the right posterior communicating artery—the right middle cerebral artery—parietal veinsis 5 sec. This is the same as via the ordinary route. There are some leptomeningeal or peripheral anastomoses between the right posterior cerebral artery and branches from the middle cerebral artery.

(*See* over for Figs. 17 and 18)

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A FIG. 17. B

Cases 135 *and* 138.—Occlusion of the left internal carotid artery (B) and high-degree narrowing of the right internal carotid artery (A). Only very slight diminishing of circulation rate through the narrowed artery.

To illustrate article by G. Nylin, B. P. Silfverskiöld, S. Löfstedt, O. Regnström and S. Hedlund.

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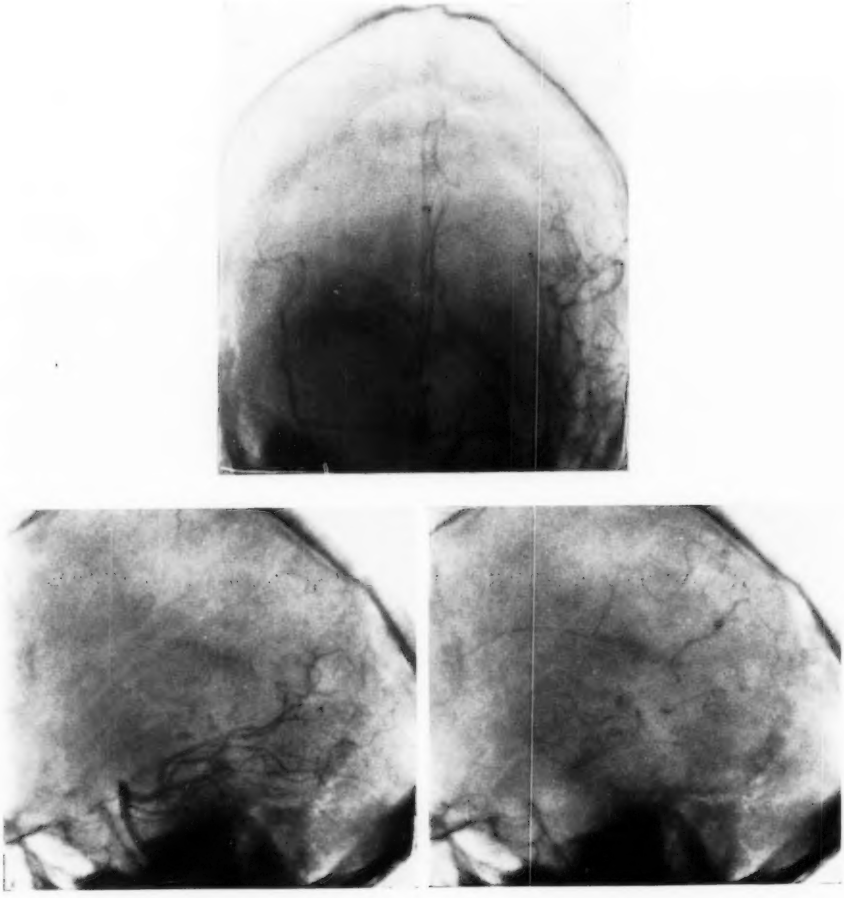

FIG. 18.

Case 115.—Total occlusion of the right carotid artery. Collateral circulation (type 1) through the anterior communicating artery. Incomplete filling of the branches from the right middle cerebral artery and the right pericallosal artery which are filled in retrograde direction via peripheral collaterals (type 3) from the right posterior cerebral artery (thus from the vertebral artery).

To illustrate article by G. Nylin, B. P. Silfverskiöld, S. Löfstedt, O. Regnström and S. Hedlund.

PHYSIOLOGICAL OBSERVATIONS IN STEREOTAXIC OPERATIONS IN EXTRAPYRAMIDAL MOTOR DISTURBANCES

BY

R. HASSLER, T. RIECHERT, F. MUNDINGER,
W. UMBACH AND J. A. GANGLBERGER

I.—Survey of Operations and Mortality

In 1947 a new era of surgery, functional neurosurgery, was initiated by Spiegel and Wycis.

Since that time stereotaxic lesions of certain subcortical structures in man have been produced in several neurosurgical centres by different techniques (Talairach, Leksell, Riechert, Narabayashi, Guiot *et al.*).

In various diseases this method is superior to open surgical intervention. Its main indication is the treatment of extrapyramidal motor disturbances. From 1950 until the end of 1958 we carried out 560 operations by means of our target apparatus, 329 of them in extrapyramidal motor disturbances. Out of these 560 cases 10 were fatal, i.e. 1·79 per cent, of the 329 cases with extrapyramidal motor disturbances 7, i.e. 2·12 per cent. 5 of these patients died due to an intra- or post-operative intracerebral hæmorrhage, one of a massive lung embolism, one of multiple hæmorrhagic infarctions of the cortex, probably secondary to penicillin therapy.

We intend to report our physiological and pathophysiological observations during stimulation and during or after high frequency-coagulation. At the same time we shall discuss the indications for the treatment and why we prefer to eliminate certain subcortical structures in extrapyramidal motor disturbances.

II.—Technique of Operation

All stereotaxic operations were performed by means of our target apparatus (Riechert and Wolff, 1950), there had, however, been some improvement based on experiences obtained from operations (Riechert and Mundinger, 1955), but the apparatus was not changed in principle in all of the 560 interventions carried out. With the aid of this instrument each point within the brain can be reached with the precision of $\pm$ 0·5 mm. It consists of a base-ring fastened by six riders on the skull of the patient, and of a semicircular arc with directing device for

electrodes. The target-point is determined on the pneumencephalographic X-ray plates.

In the determination of the target point on the pneumencephalographic X-ray plates differences of distances between the model brain and the brain of the patient are eliminated by introducing relating factors into the three dimensions of space. In this way it is possible to transfer reference measures of any subcortical target point from the model brain to the patient's brain with satisfying accuracy. To simplify the stereotaxic method the target point is respectively determined on a so-called phantom-ring, identical to the base-ring on the skull of the patient, with the determining co-ordinates. The tip of the electrode, mounted in an electrode holder on the aiming arc, is brought into touch with the phantom target point through a trephine opening marking ring. By this the different measurements are also ascertained for the patient. Without change of position of angles the complete aiming arc is then transferred to the ring on the patient and the needle electrode is inserted. Before producing a lesion within the basal ganglia the accurate location of the electrode tip is secured by X-ray check-up and electrical stimulation of the target structures is used as an additional physiological safety factor (Hassler and Riechert, 1954).

For this purpose we are using: A stimulator with double cathode-ray oscilloscope (Tönnies): Thyratron discharge (of 0·1–2 msec duration) can be triggered at any point of the sweep. By changing the sweep frequency any stimulus-rate between 1 and 500/sec may be set up. Usually we avoid stimulus frequencies higher than 100/sec in order not to elicit epileptic discharges or seizures. Strength of stimulus is controlled by different capacitors (between 3 μF and 4 μF) and by an attenuator. According to the resistance of the patient the stimulus voltage ranges from 3 to 18 V. Bipolar stimuli between tip of electrode and tip of electrode sheath (distances between 3–7 mm.) were used. The stimulus goes across a special transformer (near the electrode) which reduces the stimulus artifact by its ground-free and low capacity quality.

For special purposes we use a stimulator, which permits all forms of triangular, trapezoid or rectangular pulse forms (Tönnies). The pulse-rate changes between 0·3–500/sec. Rise and fall of pulse form can be of equal or different duration with steplike or continuous control. The pulse form can be watched on a cathode-ray oscilloscope. The high-frequency energy output goes across a special transformer and rectifier.

The elimination of subcortical structures is performed by high-frequency coagulation (Erbotom, 1·2 Mc/s, and sometimes coagulateur Wyss, 0·5 Mc/s). The extent of coagulation can be judged in relation to animal experiments. Confirmation has been given by the few brain autopsies. The diameter of the lesions can be varied from 4–9 mm. Stimulating and coagulating

electrodes are identical and insulated except for the tip and directed through an electrode sheath. The tip of the electrode has a polished length of 2 or 4 mm., and a diameter 1·2 mm. The extent of coagulation can be laterally expanded in any direction by means of a stylet electrode (diameter of 0·4 mm.), which can be driven out of the insulated lead up to 16 mm. through a lateral opening.

III.—Discussion of Target Points

In most forms of hyperkinesia, with the exception of cases of myoclonus or mere postural tremor, medial pallidal structures (pallidum internum) or thalamic relay-nuclei, neuronally connected with it, nucleus ventralis oralis anterior (V.o.a, equal to basal anterior part of VL) or nucleus latero-polaris (L.po, approximately equal to VA) were eliminated according to the following theoretical conceptions (*see* fig. 1, Plate XLV).

Patho-anatomically the true hyperkinesia are due to lesions in the striatum (putamen + caudatum), the athetoses due to additional or pure ganglion cell losses within lateral pallidal structures (pallidum externum).

If the regulating higher centres of the striatum or outer pallidal segment are out of function, the lower neuronal connected structures, especially those of the inner pallidum, are released from their physiological control. Under such circumstances the uninhibited pallidum internum is discharging uncontrolled impulses excessively. They are conducted by Forel's H_2 and H_1 (lenticular fasciculus and thalamic fasciculus) to the nucleus ventralis oralis anterior (V.o.a = anterior basal part of VL) and by another pathway to nucleus latero-polaris (L.po) thalami, the latter for its most part identical to VA of American literature. The uncontrolled impulses are transmitted to parts of area 6 and from here they descend to the peripheral motor apparatus. There they evoke the pathological patterns of muscular actions, which characterize the different hyperkinesias. Since the uninhibited impulses are conducted mostly through the relays of V.o.a (anterior basal part of VL) and L.po (VA), the elimination of these nuclei may suppress the surplus activity. (For more detailed anatomical and pathophysiological data *see* Hassler, 1949 and 1953.)

Interruption of neuronal pathways at the diencephalic level has a great advantage over cortical ablations. Subcortical afferents to area 6 are eliminated, but the so-called extrapyramidal motor areas and their efferent fibres, which run partly with the pyramidal tract, are spared, so that paralysis is avoided. In *athetoses* the removal of inhibiting influences seems to concern also deeper centres as e.g. formatio reticularis of brain-stem, which receives fibres directly from the pallidum externum. This could explain some relapses after complete unilateral elimination of the pallidum internum.

In advanced forms of mere *tremor at rest* and in all *myoclonic* hyperkinesies we chose the posterior portion of VL or of the oral ventral thalamic nucleus (V.o.p) as a target point. This thalamic nucleus (V.o.p) is the terminal relay nucleus of the fibres of the upper cerebellar peduncle (Hassler, 1949).

Patho-anatomically myoclonias are caused by a functional loss of inner cerebellar nuclei or their released excess activity due to lesions of neuronal pathways leading to them (e.g. from the inferior olives), and so uncontrolled impulses run through the efferent cerebellar pathways.

A marked influence on tremor at rest has been proved by Bucy's ablation of the precentral motor gyrus including area 4 γ and by Putnam's pyramidotomy. We therefore prefer as target point the nucleus ventralis oralis posterior (V.o.p or posterior basal part of VL), which is projecting to area 4 γ, since efferent fibres of the latter are spared and a post-operative paralysis is avoided.

In the *parkinsonian syndrome* we have coagulated since 1950 either medial pallidal structures or structures of the above-mentioned thalamic nuclei, V.o.a and V.o.p (basal parts of VL). Especially in cases of pronounced tremor at rest we preferred the V.o.a and V.o.p, while in cases of mere rigidity mostly the Pallidum internum was destroyed. In determining the target point we have taken into consideration, that the thalamo-frontal and fronto-thalamic fibres of the dominant (usually left) hemisphere, which partly pass through the V.o.a and V.o.p should be spared as much as possible, which is easier in the case of coagulation within the pallidum. For the same reason in bilateral interventions we do not coagulate in mirror-identical locations but in asymmetrical structures, on one side in the pallidum, on the other in the oral ventral thalamic nuclei (parts of VL). It can already be said, that the opinion here expressed about the patho-physiology of extrapyramidal symptoms has been proved to be correct to a considerable extent, but may in future be partly changed in the light of the steadily increasing experience in stereotaxic operations.

IV.—Results of Subcortical Stimulation with Regard to Clinical Effects and Somato-topic Representation

In our opinion, before destruction of tissue, intra-operative electrical stimulation with the inserted needle-electrode is absolutely necessary beside X-ray check up. It gives us an additional physiological proof of the exact location of the tip of the electrode. (In 9 post-mortem cases the site of the lesion produced has been proved to be correctly placed in the postulated structure.) On stimulation in the depth we observe, that with identical electrode location, beside pulse-form and impulse-rate, the initial level of motor situation and consciousness is of great importance for the effect of the stimulation. This depends on limb

position, whether it is in a resting position or raised, besides which the effect is strongly influenced by simultaneously occurring patterns of pathological movements.

(*a*) *Effects of Stimulation within the Pallidum*

In cases of parkinsonism without any tremor even stimulation of the pallidum usually fails to induce it. If tremor happens to be absent during operation it can be evoked by stimulation of the pallidum with suitable frequencies (4–8/sec, occasionally 25/sec). Slight existing tremor can be brought into step by medium stimulus frequencies, and to increasing amplitudes after a short latency (*see* fig. 2). Hence synchronisation of spontaneous tremor rhythm and stimulus frequency can often be observed with increasing and decreasing intensities of tremor. Stimulation with higher frequencies (25–100/sec) mostly reduces the intensity of tremor (*see* fig. 2, Plate XLVI) and may lead even to its complete arrest combined with flexion-synergy.

In *athetosis* and *torsion-dystonia*, stimulation with medium frequencies (4–8/sec) of the pallidum in the interval of spontaneous abnormal movements elicits the typical hyperkinetic pattern in the contralateral extremities. Higher stimulus frequencies and strengths may augment or suppress an existing spontaneous hyperkinetic pattern. This happens especially if the stimulus evokes tonic flexion of the respective limb. Active alternating movements, which the subjects perform to order (e.g. flexion and extension of arm) are slowed or stopped, mostly in medium position, especially with frequencies of 25/sec and higher. Counting to order is usually interrupted by stimulation. After stimulation subjects are not able to explain why they stopped the movements or counting. Their answers are vague; often they make lame excuses.

Patients under the influence of tranquillizers (Megaphen^R = Largactil^R, Atosil^R = Phenergan^R) show clinical arousal upon higher frequency stimulation. Responsive patients, although ordered to keep the eyes shut, usually open them, and this movement is often combined with turning of the eyes to the contralateral side, and dilatation of the pupils. Sometimes on such stimulations of pallidum we have observed inspiratory apnœa (*see* Dell, 1954), facial congestion, less frequently vomiting, outbursts of perspiration (*see* Matsui). Some patients reported oppressive feelings, mainly in the contralateral part of the chest, or a pronounced feeling of anxiety, or exhibited transient confusional states. All these phenomena occurred only during stimulation and faded away quickly. They were easy to reproduce in similar form by repeated stimulation.

(*b*) *Effects of Stimulation of the Oral Ventral Thalamic Nuclei*

Stimulation of the oral ventral thalamic nuclei (basal parts of VL) has more effect upon tremor and hyperkinetic patterns than stimulation of the

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pallidum. This may be due to the more intimate fibre connections with the motor cortex. Even single stimuli may cause an increase of spontaneous tremor amplitudes followed by a brief pause. The increase depends on the phase of tremor which the single stimulus coincides with. Even with no tremor present, single stimuli in the oral ventral nucleus (anterior basal part of VL) may produce jerks in the contralateral limbs with a steadily varying pattern of contracting muscles. This is contrary to the effect of stimulation of the posterior part of the internal capsule which, with equal needle position, is characterized by contraction of the same muscular group without latency (except neuronal conduction time). Even in the absence of tremor it may be evoked by stimulus rates of 4–8/sec.

Stimulation of the medial part of oral ventral nucleus, which was performed in cases of torsion-dystonia, frequently led to slow torsions of head, shoulder and arm, resembling the spontaneous torsion-dystonic pattern. In myoclonic cases low and high frequency stimulation of posterior part of the oral ventral nucleus may evoke typical myoclonic patterns, independent of frequency of stimulation.

While stimulating (25–50/sec) the medial or anterior part of the oral ventral nucleus we repeatedly observed turning of eyes or head to the contralateral side. Occasionally there is general excitation accompanied by indistinct verbal expressions and sudden raising of the contralateral arm. This resembles the effect of stimulation of the supplementary motor area of Penfield and Welch. With 4–8/sec stimuli applied, relatively medially close to the lamella medialis, we observed occasionally increasing drowsiness: 7 patients reported pleasant dreamlike experiences for the length of stimulation; 25–100/sec stimulation occasionally caused states resembling arousal. It was clearly marked in patients under slight anæsthesia. Some patients reported hallucinatory events.

The effects of stimulation of the oral ventral nuclei of thalamus (VL) demonstrate a somato-topical sequence of face-arm-leg from medial to lateral.

V.—Results of Subcortical and Superficial Recording of EEG

(*a*) *Intra-operative EEG Investigations*

In all patients during stereotaxic operation the EEG was recorded from the target point (bipolar between tip of needle electrode and tip of electrode sheath) and with simultaneous mono- and bi-polar leads from the scalp (Riechert and Umbach, 1955; Umbach, 1958). In 27 cases the electrical activity of the basal ganglia was recorded from 6–8 points by means of a fine multiple-wire electrode (diameter of wire 30–50 μ, 2 mm. distances between electrode-tips (fig. 3, Plate XLVII).

The spontaneous potentials recorded from subcortical structures usually show low amplitudes and fast rhythms. As shown by Hayne, Meyers, and Williams, correlated or alternating governing relations between cortical and subcortical structures, or potentials specific for certain structures, ("Feldeigenströme" of Kornmüller) could not be detected. The relatively slower potentials of the caudatum (channel 4 + 5) may be a peculiarity of this nucleus as it has been observed in animal experiments (Umbach, 1959) or in extrapyramidal diseases (Spiegel, *et al.*, 1956).

Besides the motor effects and behavioural changes mentioned above, stimulation of different subcortical structures evokes different cortical responses. Single stimuli in the anterior part (76 records) of the oral ventral nucleus (V.o.a = anterior part of VL) produce cortical responses in 69 per cent, in the posterior part (V.o.p = posterior part of VL, 24 records) in 44 per cent. Stimulation of the inner pallidum (202 records) evokes such cortical responses in only 4 per cent. The response usually consists of one (sometimes two) relatively sharp primary discharges with a latency of peak to stimulus-artefact of 15–25 msec ipsilateral and of 20–35 msec contralateral to side of stimulation (fig. 4*a*, Plate XLVIII).

Since it is most marked over the precentral region it may correspond to the specific subcortical projection to area 6*a* α (which originates in V.o.a, Hassler). Depending on the strength of the stimulus it is followed by one or two high-voltage slow waves (amplitudes 150–200 μV), which may be attributed to mechanisms of the unspecific projecting system. Statistical details of electrophysiological effects on stimulation of extrapyramidal systems will be reported elsewhere.

4–8/sec stimulation of V.o.a, and V.o.p (which are parts of VL, fig. 4*b*) show building up of discharges similar to the recruiting responses of Dempsey and Morison. With weak stimuli they are more marked ipsilaterally; with increase of strength of stimulation, they spread over all cortical areas (most pronounced over anterior regions). As stated by Dell *et al.* (1952) the patterns of response are differing in form and latency according to the spatially different projecting fibre-systems passing the V.o.a of thalamus. Synchronization and augmentation of tremor usually becomes manifest at the same time, when there is evidence of a clear recruiting.

Stimulation of the inner pallidum or V.o.a (anterior basal part of VL) with frequencies of 25/sec and 50/sec (higher frequencies usually were avoided because of the danger of inducing epileptic seizures) do not lead to desynchronization of the dominant rhythm in the EEG despite of the clinical signs resembling arousal as one would expect according to the general experience. On the contrary a period of stimulation is

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frequently followed by hypersynchronous after-potentials, single or in short groups, depending on the strength of the stimulus (fig. 4*c*).

(*b*) *Pre- and Post-operative EEG Investigations*

Comparative EEG-recordings systematically carried out before and after operation revealed besides localized abnormalities, a marked post-operative *deceleration* of the alpha rhythm. In only 16 (13·3 per cent) out of 120 thoroughly studied cases (only unilaterally operated upon) the coagulation had no decelerating influence upon the alpha rhythm (Ganglberger, 1959). The majority of these 16 patients already had records with slowed alpha rhythm prior to operation. Post-operative records revealed deceleration of alpha rhythm with decrease in frequency of 1 or 2 c/s in 75 per cent, of 3 or 4 c/s in 11·5 per cent. Records later than six weeks after operation showed complete or fairly complete recovery of the alpha rhythm to its original pre-operative frequency. Statistically no significant difference could be discovered between frequency changes after coagulations in the pallidum and in the oral ventral thalamic nuclei (VL).

Localized abnormalities (usually recorded between the sixth and eighth day after coagulation) showed individual differences. In 8 patients (6·6 per cent) out of 120, the post-operative EEG records were normal, 8 patients (6·6 per cent) showed intermittent single theta or intermittent groups of theta. The majority (104 patients i.e. 86·6 per cent) exhibited localized delta activity of different intensity (ranging from brief intermittent discharges to long irregular sequences) over the fronto-parietal or fronto-temporal region on the side of coagulation. No significant connexion between age of patient and degree of abnormality could be established. Localized abnormalities usually disappeared within six weeks after operation. Patients with pre-operative pathologically slowed alpha rhythm are more likely to show a transient organic psychosyndrome after encephalography or coagulation than those with normal alpha frequencies. The former usually show accompanying arteriosclerotic symptoms which worsen the prognosis of operation.

VI.—Effects of Coagulation and Elimination of Structures

In the course of the stereotaxic procedure it appeared desirable that the patient should be fully conscious and thus able to report about effects of stimulation or functional losses during operation. In that way it is possible to question subjects, whether during coagulation they have sensations similar to those caused by stimulation. Furthermore disturbance of motor function during coagulation can be detected in time, since the patient is able to make active movements of the limbs.

(*a*) *Within the Pallidum internum*

Most striking is the effect of coagulation upon rigidity, which can be

diminished step by step down to hypotonia. Coagulation of the middle portion (from anterior to posterior) of the pallidum eliminates rigidity of the arm. Rigidity of the leg is influenced, when the needle electrode enters further into more caudal portions of pallidum. Abnormal phenomena within the sphere of the head, e.g. oculogyric and pharyngeal crises are better removed by coagulations of the rostral portion of inner and outer pallidum. Elimination of pallidal structures may even influence tremor favourably but the effect upon tremor is not as regular and not as complete as the effect upon rigidity.

Multiple coagulations, especially of the inner pallidum extending to the outer segment may cause increasing drowsiness accompanied by decrease of tremor. Spontaneous yawning is observed and occasionally brief confusional states during coagulation. If such confusional states outlast the duration of a single coagulation, it is a sign to stop further coagulations.

Whereas the persistent therapeutic effect upon rigidity can easily be estimated during coagulation, it is more difficult to judge the lasting effect upon tremor and hyperkinetic patterns. To judge the effect achieved it will sometimes be necessary to provoke tremor or hyperkinetic patterns between single coagulations. If the degree of improvement of symptoms is not satisfactory, the straight needle electrode should be exchanged for a lateral drive-out stylet electrode through the unchanged electrode-sheet. The presence of the tip of the electrode in the vicinity of the medially situated internal capsule during coagulation elicits twitching in the contralateral facial muscles. The coagulation has to be stopped at once if the jerks include the upper limb except in cases of hemiballismus. A therapeutic effect upon rigidity and hyperkinesia should be gained without provoking such motor side-effects during coagulation.

(*b*) *Within the Oral Ventral Nuclei of Thalamus*

As can already be seen during operation tremor is more easily diminished by coagulations within the oral ventral thalamic nuclei (basal part of VL). The best effect on tremor will be gained by coagulation of the posterior portion of the oral ventral nucleus (V.o.p = posterior basal part of VL). Even a coarse and fast tremor can be stopped fairly suddenly from there. If the needle electrode is too lateral, the effects of capsular excitation may occur during coagulation, consisting of contralateral facial twitchings, occasionally also of myoclonic jerks of the arm. Such coagulations of the oral ventral nucleus (VL) may abolish a persistent tremor, without being followed by contralateral hemiparesis, with the exception of a transient facial weakness.

In order to abolish rigidity by coagulation of the thalamic structures it is necessary for the coagulation to eliminate the anterior oral ventral

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nucleus (V.o.a), especially its basal portion (anterior part of VL). In many cases the abolition of rigidity is as striking as in pallidal coagulations. Hyperkinetic patterns of the head, neck, and upper trunk sphere are more easily dealt with by coagulation of the medial portion, those of the lower half of body by coagulation of the lateral portion of the oral ventral nucleus (VL). Myoclonic jerks are best influenced by coagulation in V.o.p.

VII.—Experiences in Stereotaxic Operations in Respect to Complications and Indications

Since the main topic of this paper concerns neurophysiological observations in man obtainable by stereotaxic interventions, complications and indications will be surveyed only briefly. Damage caused by misplacing the target electrode may be avoided completely by the described technique of stimulation and coagulation. But functional losses may be caused by injured blood vessels followed by hæmorrhage or softening in the depth of the brain which are the main cause of post-operative deaths. The clinical syndrome depends on the size of the hæmorrhage. In large hæmorrhages the early symptoms are increased intracranial pressure and deep coma. The special clinical symptomatology is determined by the deep seat of the hæmorrhage. After increased intracranial pressure has disappeared we may see longer lasting pareses and psychic deteriorations.

Minor transient functional defects sometimes occur due to post-operative local œdema or vascular reaction surrounding the seat of coagulation. The most frequent symptom is a transient contralateral mimical facial weakness. Some authors suppose that the proper therapeutic effect depends on an accompanying partial damage of the inner capsule or of the pyramidal tract respectively (Bucy, 1957; Meyers, 1951). On the contrary, it must be emphasized that elimination of the symptoms of extrapyramidal motor disturbances can be achieved without injuring the pyramidal tract. Only in cases, in which as a complication the inner capsule is injured, the result is a more or less pronounced paralysis; in many cases it appears only as a transient positive Babinski's sign. Post-operative transient psychic syndromes of Bonhoeffer's exogenic reaction-type may occur in arteriosclerotic patients as a sign of diffuse cerebral alterations. In such cases these syndromes may already be provoked by pneumencephalography and differ clearly from psychical symptoms due to local post-operative œdema.

Coagulations within the oral ventral nuclei of the thalamus may be followed by transient disturbances, resembling a frontal lobe syndrome, due to additional lesions of thalamo-frontal pathways. They soon disappear in unilateral coagulations. And we avoid bilateral symmetrical thalamic coagulations. In unilateral pallidal coagulations psychical

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deteriorations occur much less often and are less uniform. The following are our conclusions on the results of, and indications for, the treatment.

In the parkinsonian syndrome the rigidity can be reduced to a minimum in nearly all cases. A remarkable decrease in or even disappearance of the tremor may be accomplished, but not with the same certainty and completeness as in the case of rigidity. The rare cases of pure akinesia show the lowest chance of success, while post-encephalitic compulsive phenomena including oculogyric crises respond favourably. In a parkinsonian syndrome, complicated by cerebral arteriosclerosis or increased blood pressure, one has to be careful in deciding the indication for stereotaxic intervention owing to reduced ability of cerebral compensation, increased danger of intra-operative hæmorrhage and post-operative vascular and lung complications.

As to the hyperkinesia, one has to be careful in Huntington's chorea because of the greater risk of complications, especially if there are already psychical deteriorations or vegetative disturbances. Even in such cases, however, there is a good possibility of influencing the hyperkinetic pattern for the better.

Torsion dystonia may be much improved by stereotaxic intervention. If the muscular spasms merely concern the musculature of neck w recommend peripheral interventions first.

According to the severity of the symptoms athetosis can be moderated up to a certain degree. But there is a high tendency to relapse. The younger the patient the better the prognosis.

The stereotaxic coagulation of V.o.p (posterior basal part of VL) produces a good effect in myoclonic syndromes. But in cases of myoclonus epilepsy we should advise against any interventions because of the rapid progress of the underlying pathological process.

Summary

Experiences based on 329 stereotaxic interventions in extrapyramidal motor disturbances (1950–1958) have been reported. They concern especially neurophysiological observations during stimulation as well as during and after elimination of pallidal structures and the oral ventral nuclei of thalamus, and intra-operative electro-encephalographic findings.

The effect of stimulation of the inner pallidum upon the appearance and pattern of hyperkinesia and tremor depends on stimulus-frequency and initial situation. Single stimuli elicit twitching in the contralateral limbs of varying muscular pattern. Higher stimulus-rates may increase the tremor or block it. Active alternating movements and the utterance of sequences are slowed or blocked. Higher stimulus frequencies cause slow flexions of contralateral arm, opening and turning of eyes to the contralateral side, resembling clinical arousal, or sometimes transient

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interruptions of continuity of consciousness. Coagulations abolish or reduce rigidity and even the tremor. At the end of coagulations of greater parts of pallidum transient drowsiness, decrease of spontaneity and perhaps brief confusional states may occur.

Stimulations of oral ventral nuclei of thalamus (which correspond with VL) show an even greater effect upon tremor and hyperkinetic patterns. 4–8/sec stimulation of these nuclei may cause a tremor at rest and recruiting-like discharges over the whole ipsilateral hemisphere (in case of stronger stimuli over both hemispheres) mainly in the frontal region. Clinical states resembling arousal were not accompanied by desynchronization of EEG rhythms. Higher frequency stimuli may elicit acceleration of active alternating movements, sometimes a behavioural effect as described from the supplementary motor area. Elimination of these thalamic nuclei results in abolition or marked decrease of tremor and rigidity and of hyperkinetic patterns. Tremor at rest and myoclonus respond best to coagulation of the posterior portion of the oral ventral nucleus (V.o.p or of VL).

After coagulation local EEG abnormalities on the side of operation and general deceleration of alpha rhythm were usually found but disappeared within six weeks.

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LEGENDS FOR PLATES

PLATE XLV

FIG. 1.—Schematic drawing of the extrapyramidal neurone systems in their connexion with the motor cortex and the peripheral motor apparatus. In order to abolish hyperkinesia or rigidity the afferent neurone systems of area 6 a α and 6 a β are interrupted either within the inner part of pallidum or within the anterior oral ventral nucleus of thalamus (V.o.a) respectively within the latero-polar thalamic nucleus (L.po). Hereby the surplus activity, which causes the peripheral extrapyramidal symptoms, is intercepted already at the subcortical level. The flux of uncontrolled impulses within the efferent systems from area 6 a α and 6 a β to the anterior horn apparatus of the spinal cord is then reduced. The afferent systems of area 4 are interrupted within the nucleus ventralis oralis posterior (V.o.p), if tremor at rest or myoclonic hyperkinesia is to be influenced.

A = Nucleus anterior thalami
Br. cj. = Brachium conjunctivum.
Cd. = Caudatum
Ce = Centre médian
Dt = Nc. dentatus
Eb = Nc. emboliformis
F. rt = Formatio reticularis
L.po = Nc. lateropolaris thalami

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M. = Nc. medialis thalami
Ni = Nc. niger
Pall. e. = Pallidum externum
Pall. i. = Pallidum internum
Put = Putamen
Py = Pyramidal Tract
Ru = Nc. ruber
V.c = Nc. ventro-caudalis thalami
V.o.a = Nc. ventralis oralis anterior thalami
V.o.p = Nc. ventralis oralis posterior thalami

PLATE XLVI

FIG. 2.—Tremor-registration (channel 6) and scalp–EEG during stimulation of right Pall. intern. in Parkinson's disease (8-channel Schwarzer apparatus : 1–5 unipolar against homolateral ear, 7+8 bipolar; Thyratron–stimuli of 0·5 msec duration : 8/sec-stimuli approx. 4·5 V, 50/sec-stimuli 1, 3 V). With 8/sec-stimulation (left half), slight spontaneous tremor is augmented after a short latency, then the tremor rate is altered. With 50/sec-stimulation intensity and rapidity of tremor is reduced, sometimes blocked for 3–5 seconds after the end of stimulation.

PLATE XLVII

FIG. 3.—Registration of left subcortical structures with a multi-wire electrode (channel 1–5) and bipolar scalp–EEG (channel 6–8) in a patient with Parkinsonian disease (Calibration: Left half 1/3 of the right: 7 mm. = 50 μV). There is nearly no phase-difference of scalp-EEG and subcorticogram except some phase reversal between Caps. interna (3 channel) and precentral region (channel 6+7). Subcortical structures usually show faster rhythms.

PLATE XLVIII

FIG. 4.—Scalp–EEG (channel 1–6 unipolar against homolateral ear, 7+8 bipolar), stimulation in V.o.p dext., hemiparkinsonism. (*a*) 1/sec-stimuli produce evoked potentials with one or two spikes (latency 15–25 msec on the ipsilateral side, 20–35 msec on the opposite one) and a high-voltage (150–200 μV) slow wave (monophas. in the unipolar, biphas. in the bipolar derivation), especially over the stimulated hemisphere. (*b*) 8/sec-stimuli produce recruiting-like responses with waxing and waning over the ipsilateral hemisphere, less pronounced over the contralateral hemisphere. Tremor is blocked at first for 1-1 1/2 second, then accelerated and reinforced for the time of stimulation (*see* fig. 2). (*c*) 25/sec-stimulation blocks the tremor. Drowsy patient is aroused, opens the eyes, looking to the left. No desynchronization or attenuation effect in the EEG.

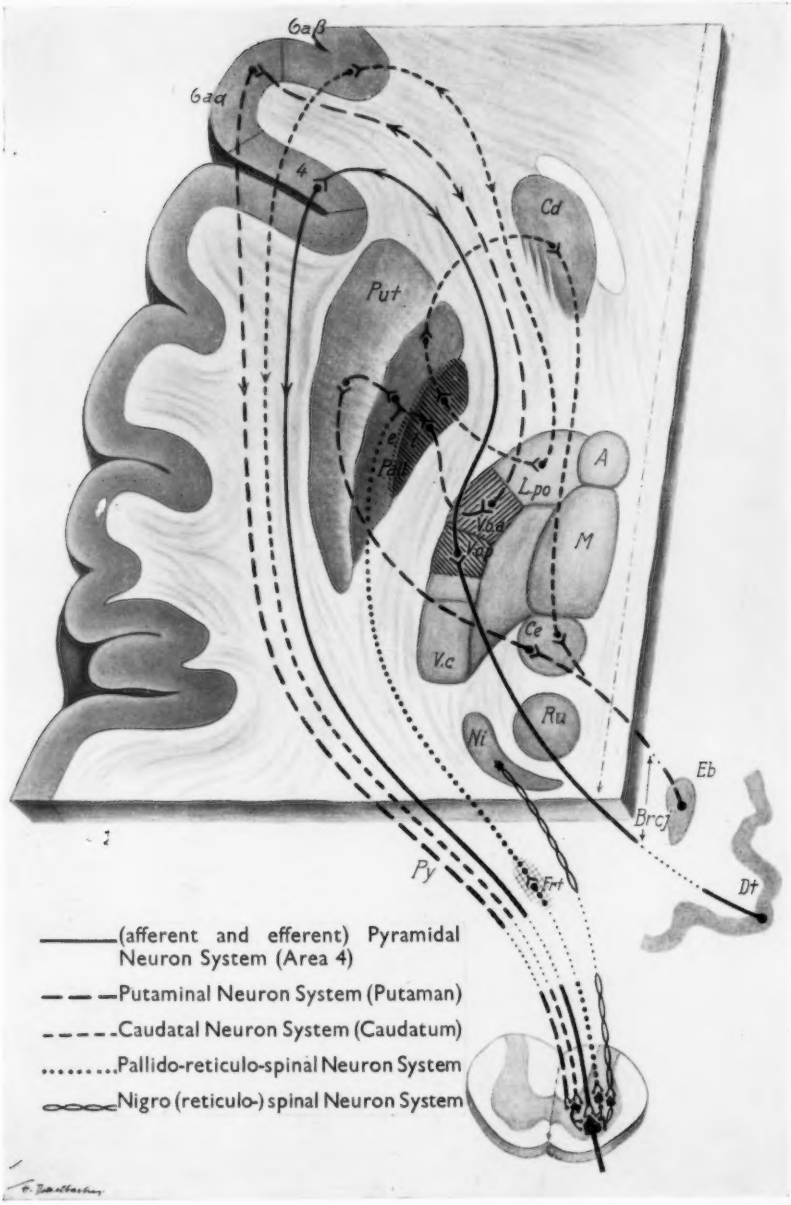

FIG. 1.

To illustrate article by R. Hassler, T. Riechert, F. Mundinger, W. Umbach and J. A. Ganglberger.

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PLATE XLVI

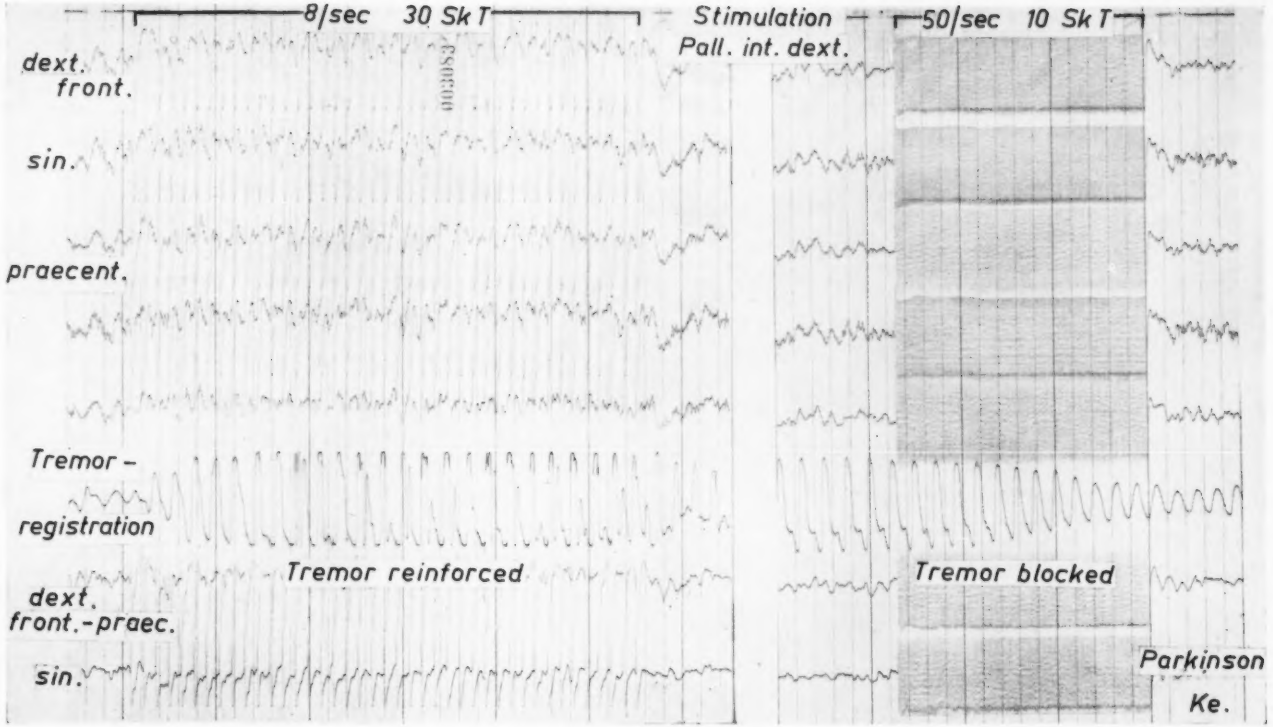


FIG. 2.

To illustrate article by R. Hassler, T. Riechert, F. Mundinger, W. Umbach and J. A. Ganglberger.

PLATE XLVII

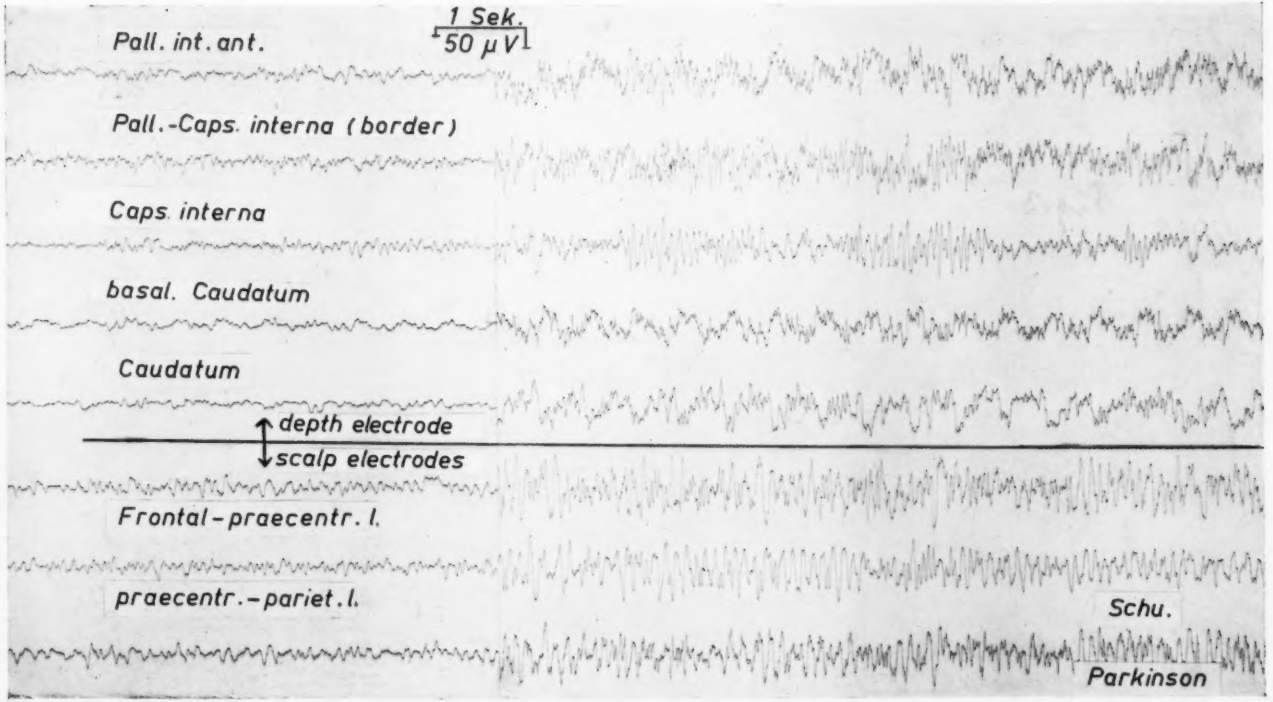
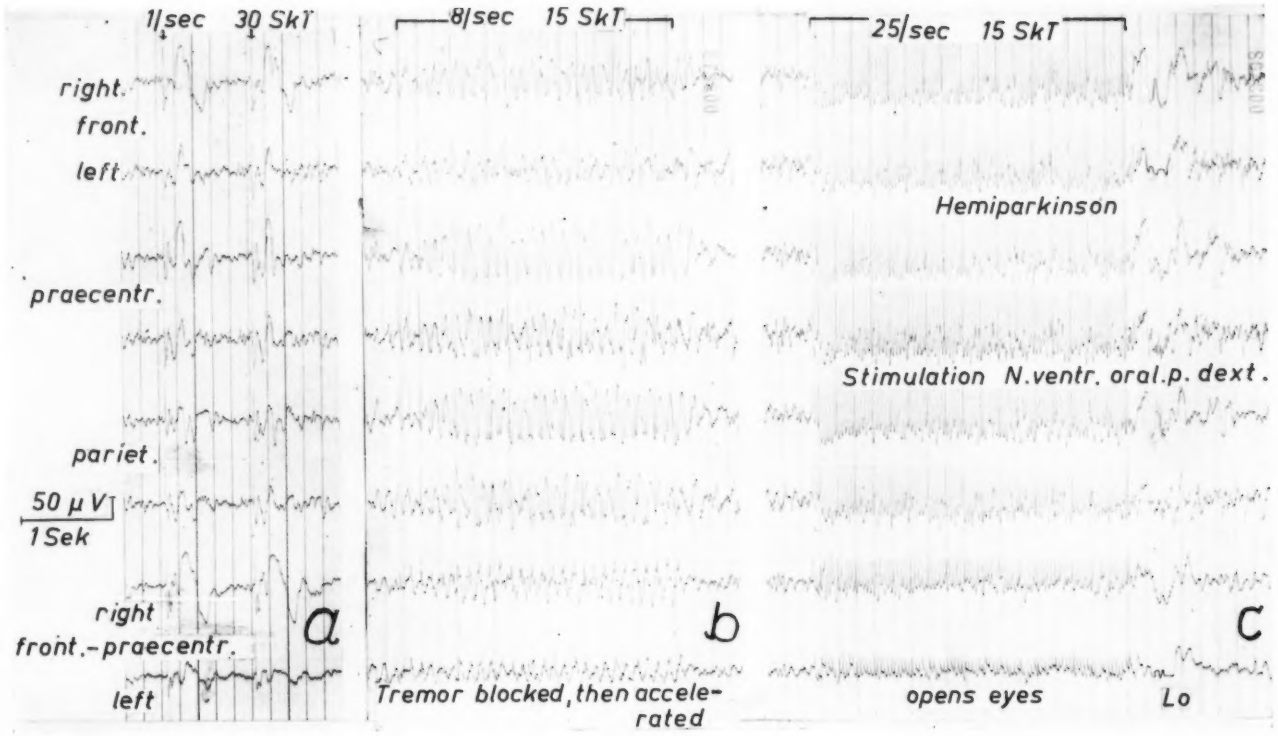


FIG. 3.

To illustrate article by R. Hassler, T. Riechert, F. Mundinger, W. Umbach and J. A. Ganglberger.



FIG, 4.

To illustrate article by R. Hassler, T. Riechert, F. Mundinger, W. Umbach and J. A. Ganglberger.

NOTICES OF RECENT PUBLICATIONS

THE CORPUS CALLOSUM

Les Agénésies du Corps Calleux. By FRANCIS ROHMER, with the collaboration of Auguste Wackenheim and Constantin Vrousos. 1959. Pp. 144. Paris: Masson et Cie.

The corpus callosum, the largest of all fibre tracts in the brain, must have highly important functions in relating and co-ordinating the activities of the two cerebral hemispheres. Yet there is a wide discrepancy between the anticipated and the actual effects of damage to this structure in man and animals. Detailed studies of patients with agenesis of the corpus callosum may eventually contribute to the resolution of this enigma.

This monograph is based on a clinical and radiological study of 21 cases of agenesis of the corpus callosum which were observed in the department of neurology in Strasbourg in the past ten years. The results were presented at a conference of neurologists and psychiatrists in Tours in June 1959.

There is a preliminary review of the development and structure of the corpus callosum with a description of the varying degrees of agenesis which have been recorded since Reil's original account in 1812. This is followed by an account of the apparently negligible effects of section of the corpus callosum in animals and man and a description of the modes of clinical presentation of patients with defects of the corpus callosum. The majority of patients present in infancy and childhood with retardation and epilepsy. In adults intelligence is usually normal and the diagnosis usually emerges during investigation of epilepsy of late onset. Fits are focal in a high proportion of cases. In recent years carotid arteriography has contributed to the identification of some of these adult cases by outlining the altered position and course of the anterior cerebral and pericallosal arteries but air encephalography remains the standard means of diagnosis. Electroencephalography has contributed little so far. Bilateral synchrony persists.

The authors devote considerable attention to the encephalographic signs so well described by Davidoff and Dyke in 1934 and have some interesting observations to make concerning the enlargement and deformities of the supra-pineal recess in cases of agenesis of the splenium of the corpus callosum. The illustrations and line drawings in this section of the monograph are particularly interesting. There follows a summary of 21 cases which were studied, in 5 of which the diagnosis was confirmed by operation. There are no pathological reports. In 9 cases agenesis of the splenium of the corpus callosum was diagnosed on the basis of dilatation of the supra-pineal recess, altered position and course of the internal cerebral vein, asymmetrical abnormalities on the electroencephalograph and, rarely, with difficulties in visual discrimination. The authors conclude that further clinical tests may be devised which will reveal subtle difficulties experienced by patients with partial agenesis of the corpus callosum. The corpus callosum is there, we know little of its function, and absence of gross symptoms when it is divided in animals or even in man must not be taken to mean that it has no normal functions.

JOHN D. SPILLANE.

ALLERGIC ENCEPHALOMYELITIS

Experimental Allergic Encephalomyelitis and the "Auto-allergic" Diseases. By B. H. WAKSMAN. (Supplementum to Vol. 14, International Archives of Allergy and Applied Immunology.) 1959. Pp. 87. Basel and New York: Karger. Price S.Fr. 15.

The widespread clinical interest in experimental "allergic" thyroiditis and the current clinical acceptance, based on the demonstration of circulating antibodies, that

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Hashimoto's disease is the human counterpart of the experimental disease, have given tremendous impetus to the concept of auto-antibody mechanisms as a cause for many other disease states and the concept promises fair to become abused as a facile explanation for all inflammatory processes not actually caused by the presence of living bacteria or viruses. The appearance therefore of a short comprehensive survey from the pen of a single author attempting a synthesis and critical examination of the group as a whole is timely. No one is better qualified to attempt this than the author, Dr. Byron Waksman, who is Associate Professor of Immunology at Harvard Medical School, and who has made important original contributions in this field over the past ten years. This is an eminently factual description of the histological and immunological features of the group of experimental, presumptively auto-allergic diseases comprising encephalomyelitis, radiculoneuritis, uveitis, orchitis, adrenalitis, thyroiditis, phako-anaphylactic endophthalmia, and Voisin and Maurer's form of dermatitis.

There is little one could quarrel with in the individual accounts although, for instance, on page 42, in regard to the question of the local versus hæmatogenous origin of the cells in the inflammatory infiltrates it might have been mentioned that there is at least some indubitable local proliferation of cells in the venular walls as witnessed by the not infrequent occurrence of mitotic figures. The much-needed reasons for defending the view that these experimental diseases are all the direct sequel of an immunological reaction are fully adduced and well argued. It would be absurd to claim—nor does the author of this essay seek to claim—that the biological mechanism underlying the experimental auto-allergic processes is understood. But the hypothesis which he and others offer for the encephalomyelitis, and which authors including Witebsky and Rose have offered for the experimental "auto-allergic" thyroiditis, consistently fails, in the reviewer's way of thinking, in overlooking one important fact, namely that the type of cell which is locally-produced in the target organ is the reticulum or pre-plasma cell. Its local production would seem to be unnecessary on the circulating-antibody-hypothesis, whether the antibody in the circulation were free or bound to lymphocytes.

Inevitably in a field of intensive research such as this the review is already out of date in some important details. For instance, the statement, more than once, that passive transfer has not been successful ante-dates Paterson's recent elegant experiments. Likewise, in the section on experimental allergic neuritis, the guarded statement about possible antigenic differences between brain and peripheral nerve would now need amplification by the recent evidence of Robertson that bovine cord contains specific encephalitogenic protein which migrates to the cathode in an electrical field and which is absent from brain.

On the significance of these experimental diseases to human disease, the author is evidently on less familiar ground and is apt to make dogmatic statements based on the publications of others chosen to suit his thesis. His statement, for instance, that "it is fair to say that the principal features of each of" . . . "the human demyelinative diseases" . . . "except Schilder's disease have been duplicated in animals with allergic encephalomyelitis" is based largely on the views of Roizon and Ferraro and begs a large question indeed which there would be no time to answer here. Likewise, the statement (page 13) that Honor Smith's results are "not interpretable" is an opinion of the author which the reviewer does not share.

These minor criticisms merely serve to say that Waksman's review is stimulating and provocative, quite remarkably comprehensive for its eighty pages, and, in fact, irreproachably objective considering the intensely exciting nature and importance of this curious disease mechanism. The printing is of high standard, the photomicrographs of great clarity, and proof-reading and the preparation of the reference list faultless as far as the reviewer could see.

C. E. LUMSDEN.

THE CEREBROSPINAL FLUID

Der Liquor Cerebrospinalis im Kindesalter. By Professor Dr. H. SCHÖNENBERG. 1960. Pp. 175. Stuttgart: Georg Thieme Verlag. Price DM. 29.

Few monographs in German on the cerebrospinal fluid have appeared and this one by Professor H. Schönenberg is an attempt to remedy this omission. The volume is divided into two parts, the first and larger being concerned with the methods of examination and the results of such examination on the normal fluid. The smaller portion is concerned with the abnormalities found in fluids from patients with various neurological diseases, but more especially in infections.

It is of some interest that almost all the methods employed are of German origin, but to some this may have a special interest as when the author describes the Mastic Colloidal reaction or the Kapka-Samson technique for protein determination. Electrophoretic techniques for protein analysis are also well described.

A table of normal values for many substances in both blood and cerebrospinal fluid is given but not all workers would agree with some of the figures, such for instance as magnesium and creatine.

Rather too much attention is given in the second part, which is devoted to disease processes, to the infections in view of the relative decrease in the number of these conditions at the present time.

A very extensive and valuable list of references is appended. The volume will be of value to those who are interested in the composition of the cerebrospinal fluid and the techniques that are commonly employed on the Continent. J. N. CUMINGS.

PERIMETRY

The Essentials of Perimetry. By HOWARD REED, F.R.C.S., with a Foreword by Arnold Sorsby, M.D., F.R.C.S. Oxford University Press. Pp. 192. Price 45s.

This book is based on lectures at The Royal Eye Hospital. It is divided into three parts, the first for the applied anatomy of the visual pathway, the second for the visual field and its assessment, the third for field defects and their interpretation. There is an excellently clear and well-illustrated exposition of the anatomical features of the visual pathway in its anterior parts. The description of the field examination emphasizes the author's preference for confrontation tests rather than perimetry which he describes as "of little value for diagnosis except in cases of retinitis pigmentosa or rare cases with defects situated outside the thirty degree isopter."

The field defects of diseases which the ophthalmologist is likely to meet are very well covered. The neurological disorders are less well handled and give the impression that the author's neurological experience is much less than his ophthalmological. In a book of this title the balance needs to be better. The work needs modification and extension before it can be considered neurologically satisfactory: but should be very useful ophthalmologically in its present form. WILLIAM GOODDY.

PSYCHOLOGICAL METAMORPHOSIS

Metamorphosis. By ERNEST SCHACHTEL. 1959. Pp. 344. New York: Basic Books. Price $6.

The "metamorphosis" of the title is that of man from the embryo to the adult, and the theme of this book is the problem of how adult man with his capacities and limitations becomes what he is. The author is analytically orientated but seeks to modify classical Freudian theory. Freud's view was that the infant strives only for the reduction and discharge of tension, governed only by the pleasure-pain principle. Dr. Schachtel argues that the new-born infant has also another tendency. He has an impulse to turn towards the world, to be attracted by a variety of stimuli and to develop increasing capacity for active searching for satisfaction. There exists therefore, besides

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the regressive tendencies emphasized by Freud, tendencies to emergence, and the adult personality develops from the conflict between these.

The author applies his theory to the development of affect, perception, attention and memory. These are basic problems of psychology and it is refreshing to see how he draws for material not only upon philosophy and literature but also upon experimental psychology.

This is a stimulating book which may widen the somewhat narrow bases of psychoanalytic theory and counterbalance Freud's pessimism. ELIOT SLATER.

PSYCHOPHARMACOLOGY

Psychopharmacology Frontiers. By NATHAN S. KLINE. 1959. Pp. 533. London: J. and A. Churchill. Price 72s.

Of recent years there has been a great development of medical congresses, often involving several hundreds of people and utilizing modern methods of communication, I.B.M. instantaneous translations and all. The papers presented and the subsequent discussions are then published, often some considerable time later, in pedantic detail. This book reports the Proceedings of the Psychopharmacology Symposium of the Second International Congress of Psychiatry held in Zurich in September 1957. Sixty-five papers were presented, the bulk of which consist of dreary descriptions of how a drug, usually reserpine or chlorpromazine, was administered to ten, a hundred or a thousand or more patients, some of whom improved and the others did not. The majority of these papers would not be accepted by a reputable journal. It would, however, be rash to draw conclusions from the fact that of the 93 participants only one is working in the United Kingdom. ELIOT SLATER.

INSULIN TREATMENT

Insulin Treatment in Psychiatry. Ed. M. RINKEL and H. E. HIMWICH. 1960. Pp. 386. London: Peter Owen. Price £1 15s.

This volume reports the proceedings of the International Conference on Insulin Treatment in Psychiatry held at the New York Academy of Medicine in October 1958. The story of the introduction of insulin coma treatment is followed by an account of biochemical and EEG changes during hypoglycæmia. The major part of the book is concerned with evaluation of insulin treatment, and provides yet another example of the conflict between the results of clinical experience and controlled trials in the drug treatment of disease. Work in progress foreshadowed here is, however, likely to provide generally accepted conclusions on the place of drugs and of insulin in the treatment of the various categories of schizophrenia. R. T. C. PRATT.

BIRD-HEADED DWARFS

Bird-headed Dwarfs. Studies in developmental anthropology including human proportions. By H. P. G. SECKEL. 1960. Pp. 241. Basel and New York: Karger. Price S.Fr. 54.

In addition to extreme dwarfism, nanocephalic dwarfs show microcephaly with a cranial capacity of 400+ to 640 c.c. and a degree of mental retardation considerably less than that of the typical microcephalic idiot; a bird-like facies due to the large size of the nose, and in some instances associated congenital abnormalities. The author of this monograph describes 2 typical cases in detail, comparing them with normal anthropological data, and reviews 13 others from the literature between 1746 and 1951. (A more careful search might have added others, e.g. *Proc. Roy. Soc. Med.*, 1931–2, **25**, 416.) The author inclines to the view that dwarfism was due to a single-locus recessive gene, "with pleiotropism for smallness of brain and head, faulty embryonal

differentiation of many organs and a sublethal outcome." The differential diagnosis from hypothyroid and hypopituitary dwarfism, normocephalic primordial dwarfism and progeria is considered.

RICHARD W. B. ELLIS

SHORTER NOTICES

Neurological Complications of Lymphomas and Leukemias. By H. M. WILLIAMS, M.D., H. D. DIAMOND, M.D., L. F. CRAVER, M.D., and H. PARSONS, M.D. 1960. Pp. 134. Oxford: Blackwell. Price 43s.

13 per cent of nearly 6,000 patients with these diseases had involvement of the nervous system ranging from herpes zoster to complete paraplegia. The most serious complication was spinal cord compression usually by an extra dural tumour, sometimes with vertebral collapse. Of 118 patients of this sort, one-third had a complete paraplegia, constituting a neurosurgical emergency. Involvement of peripheral nerves in the disorder responds to specific treatment, and diffuse peripheral neuropathy occurs. An unusual complication is invasion of the nervous system by *Cryptococcus neoformans.*

The Neurological Examination. By RUSSELL M. DEJONG, M.D. Second Edition. Pp. 1078. London: Pitman Medical Publishing Company. Price £7.

This very large text includes the fundamentals of neuro-anatomy and neurophysiology, and it provides a source book for the advanced teacher in neurology, though Dr. DeJong states that the text follows the lectures on the neurological examination that are given to junior and senior students in the University of Michigan Medical School. The logical emergence of diagnostic procedures from neurological anatomy and physiology makes the text a dynamic one. With such a wealth of clinical detail, however, it must have been difficult for the author to exclude nosological description. The index is excellent, the material accurately presented, and this second edition as inclusive as its predecessor eight years ago.

NOTICES OF FORTHCOMING CONFERENCES

SECOND INTERNATIONAL CONGRESS OF NEUROLOGICAL SURGERY

THE Second International Congress of Neurological Surgery will be held at the Hotel Statler, Washington, D.C., October 14 to 20, 1961. This conference is sponsored by the World Federation of Neurosurgical Societies, founded at Brussels, in 1955. The First International Congress of Neurological Surgery was held in Brussels in 1957.

The Federation is presently composed of 25 national neurosurgical societies representing 50 nations. More than a thousand neurosurgeons from all parts of the world are expected to attend the Washington meeting.

Four morning sessions will be devoted to symposia on the following topics:

I. Radioactivity and Heavy Radiation Particles in Neurosurgery.
II. Space-occupying Intracranial Lesions.
III. Re-evaluation of Surgery in the Treatment of Pain.
IV. *A.* Biology of the Nervous System.
B. Hydrocephalus.

Voluntary papers are scheduled for presentation in the afternoons. A special feature will be daily television programs of operative procedures and panel discussions on neurosurgical techniques.

All inquiries and correspondence should be sent to:

Dr. BRONSON S. RAY, *Secretary-General,*
525, East 68th Street,
New York, 21, N.Y., U.S.A.

XUM

IX. Latin American Congress of Neurosurgery. This Congress will be held in Mexico City, Mexico, from October 4 to 10, 1961.

INTERNATIONAL SYMPOSIUM

"THE EXTRAPYRAMIDAL SYSTEM AND NEUROLEPTICS"

THE Department of Psychiatry of the University of Montreal is organizing an international symposium on "The Extrapyramidal System and Neuroleptics" to be held at the University of Montreal on November 17, 18, and 19, 1960. This symposium will permit an exchange of ideas among those researchers interested in this subject from the point of view of anatomy, physiology, neurosurgery and psychiatry. Admission to the symposium will be unrestricted but participation will be by invitation only. We will have the co-operation of our ten Canadian provinces, the United States and several European countries. There are two official languages, English and French, with simultaneous translation. For information, address to:

Doctor JEAN-MARC BORDELEAU,
Department of Psychiatry,
University of Montreal,
Montreal, Canada.

NEW JOURNALS

THE following are new journals or old journals in a new form.

Psychiatric Research. Editor in chief Seymour S. Kety, National Institute of Mental Health, Bethesda, 14, Maryland, U.S.A. Published by Pergamon Press, New York, London, Paris, Los Angeles. Has been "founded as a contribution towards meeting growing need for research of high quality in the field of mental illness and mental health." Subscription £7 per volume for libraries, government establishments and research institutions, £5 per annum for individuals who write directly to the publishers and certify that the journal is for their personal use.

World Neurology. Editor in chief, Charles M. Poser and published by Lancet Publications Inc., 84, South 10th Street, Minneapolis, Minnesota, U.S.A. Is the official journal of the World Federation of Neurology and is to appear in July 1960. Subscription $15 per annum.

Epilepsia. Editor in chief Sir Francis Walshe. Has been taken over by the Elsevier Publishing Company, Amsterdam (English distributors, Messrs. D. van Nostrand Company, Limited, 358, Kensington High Street, London, W.14). Subscription £2 17s. per annum.

The International Journal of Neurology. Chief editor Victor Soriano Calle, Buenos Aires, 363, Montevideo, Uruguay. Subscription $10 per annum. Will contain articles written in English, French, German and Spanish with a summary in the remaining languages. Each number will deal with one subject, the first being dedicated to epilepsy.

Russian Review of Biology. Editor in chief, G. K. Krushchov. Now appears in an English translation, publishers, Oliver and Boyd Limited, Tweeddale Court, 14, High Street, Edinburgh, 1. Subscription £6 10s. per annum.

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